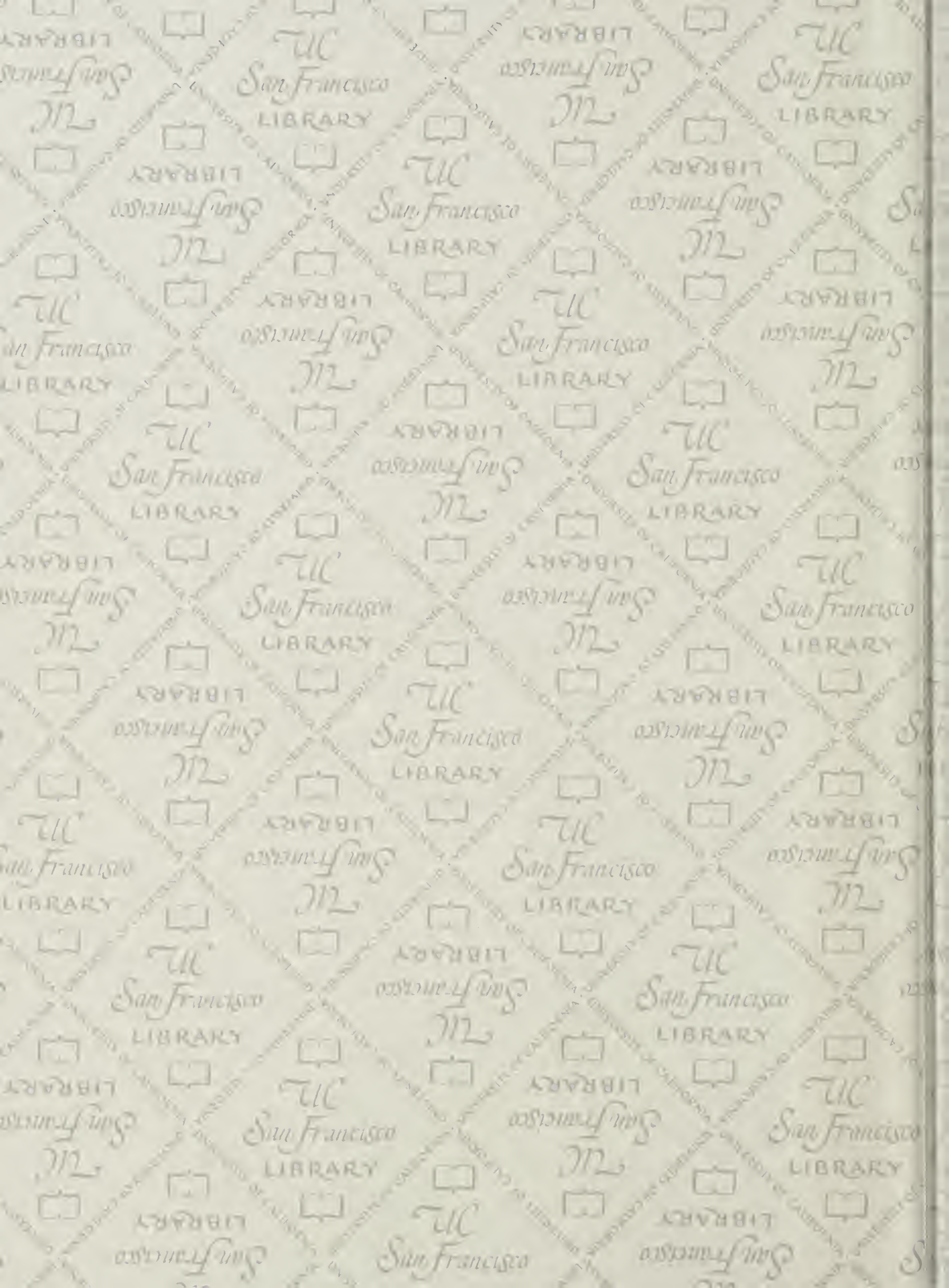
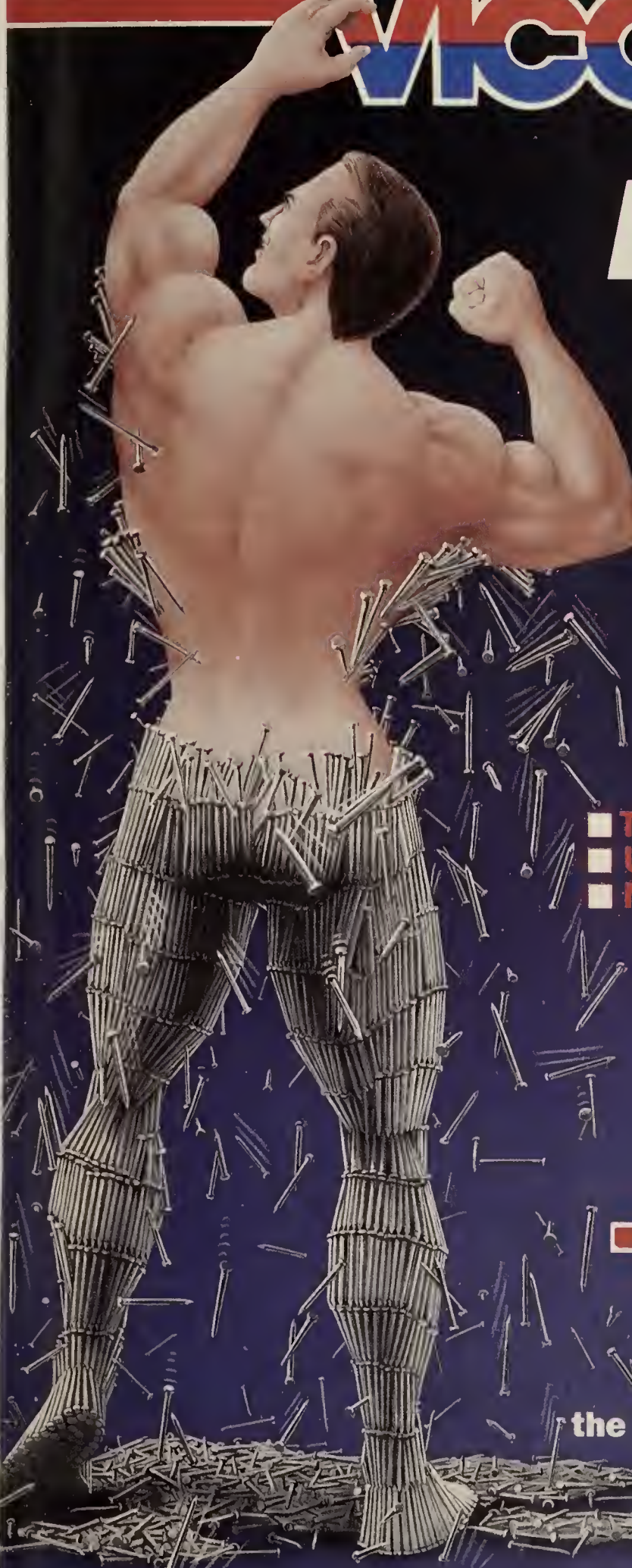




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* (hydrocodone bitartrate 7.5mg [Warning: May be habit forming] and acetaminophen 750 mg)

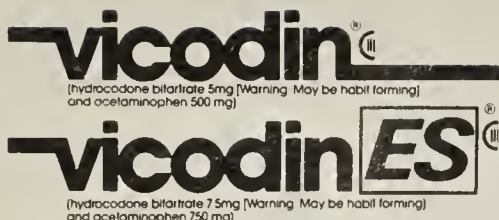
**Tablet for tablet,
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** (hydrocodone bitartrate 5 mg [Warning: May be habit forming] and acetaminophen 500 mg)

1. Data on file, Knoll Pharmaceuticals

2. Standard industry new prescription audit.

Please see adjacent page for brief summary of prescribing information.



INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.

WARNINGS:

Allergic-Type Reactions: VICODIN/VICODIN ES Tablets contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS:

Special Risk Patients: VICODIN/VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when VICODIN/VICODIN ES Tablets are used postoperatively and in patients with pulmonary disease.

Drug Interactions: Patients receiving other narcotic analgesics, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with VICODIN/VICODIN ES Tablets may exhibit an additive CNS depression. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy:

Teratogenic Effects: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN/VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever.

Labor and Delivery: Administration of VICODIN/VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN/VICODIN ES Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence and mood changes.

Gastrointestinal System: The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN/VICODIN ES Tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

DRUG ABUSE AND DEPENDENCE:

VICODIN/VICODIN ES Tablets are subject to the Federal Controlled Substance Act (Schedule III). Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN/VICODIN ES Tablets should be prescribed and administered with caution.

OVERDOSAGE:

Acetaminophen Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post ingestion.

Hydrocodone Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

MEETINGS AND LECTURES

The New York State Journal of Medicine cannot guarantee publication of meeting and lecture notices. Information must be submitted at least three months prior to the event.

FEBRUARY 1991

AROUND THE STATE

MANHATTAN

Feb 7. The Adult With Congenital Heart Disease. 2 Cat I Credits. New York Helmsley Hotel. Contact: The New York Cardiological Society, Inc, 681 Lexington Ave, Suite 310, New York, NY 10022. Tel: (212) 888-5595.

MANHASSET

Feb 1. Aging and Depression: Confronting the Challenge. North Shore University Hospital. Contact: Linda Haberman, MA, Coordinator, Senior Citizen Programs, Dept of Health Education/Community Affairs, North Shore University Hospital, 300 Community Dr, Manhasset, NY 11030. Tel: (516) 562-3045.

AROUND THE NATION

CALIFORNIA

Feb 1-2. Second Annual Pediatric Dermatology for the Primary Care Physician. 10 Cat I Credits. **Feb 15-17. 24th Annual Recent Advances in Neurology.** 15 Cat I Credits. San Francisco. Contact: Extended Programs in Medical Education, University of California, Room C-124, San Francisco, CA 94143. Tel: (415) 476-4251.

COLORADO

Feb 2-9. 17th Annual Vail Conference in Anesthesiology. 25 Cat I Credits. Marriott's Mark Resort, Vail. **Feb 9-16. 16th Annual Vail Symposium in Intensive Care.** 25 Cat I Credits. Marriott's Mark Resort, Vail. Contact: Professional Seminars, Inc, PO Box 012318, Miami, FL 33101. Tel: (305) 547-6411.

Feb 2-9. Eighth Annual Office Based Sports Medicine. 27 Cat I Credits. Snowmass Conference Center, Snowmass. Contact: Extended Programs in Medical Education, Registration Office, Room LS-105, University of California, San Francisco, CA 94143. Tel: (415) 476-5808.

DISTRICT OF COLUMBIA

Feb 28-Mar 2. Children's Defense Fund Annual National Conference. Washington Hilton Hotel. Contact: Children's Defense Fund, 122 C St, NW, Washington, DC 20001. Tel: (202) 628-8787.

FLORIDA

Feb 11-13. 14th Annual Gold Coast Ob/Gyn Conference: Clinical Trends in Ob/Gyn. 12 Cat I Credits. Good Samaritan Hospital, West Palm Beach. **Feb 21-23. 14th Annual Gold Coast Surgery Conference: On the Cutting Edge: Technological Advances for the Surgeon.** 12 Cat I Credits. Good Samaritan Hospital, West Palm Beach. Contact: Laura J. Lehmann, CME Coordinator, Good Samaritan Health Systems, Inc, PO Box 024308, West Palm Beach, FL 33402. Tel: (407) 655-5511.

Feb 14-17. Mammographically Detected Early Breast Cancer: Current Concepts and Controversies in Diagnostic Management. Ritz-Carlton Resort Hotel, Naples. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077. Tel: (404) 641-9773.

AROUND THE WORLD

ANTARCTICA

Feb 19-Mar 5. Medicine in the Extreme Environment. Contact: Marian Papp, Executive Director, Seminars & Symposia, Inc, 132 East 70th St, New York, NY 10021. Tel: (212) 517-7520.

PUERTO RICO

Feb 11-15. Current Topics in Diagnostic Imaging. 23 Cat I Credits. Hyatt Regency, Cerromar Beach. Contact: NYU Medical Center, Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295. □



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HYPERTENSION UPDATE

The 1988 Joint National Committee Report

1988 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends that blood pressure be controlled:

"...with the fewest drugs at their lowest dose...."¹

180 mg

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- A recommended dose for initial therapy*

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References: 1. 1988 Joint National Committee: The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988;148:1023-1038. 2. *Physicians' Desk Reference*, ed 44. Oradell, NJ, Medical Economics Company inc, 1990.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil. **Warnings:** Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdose. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

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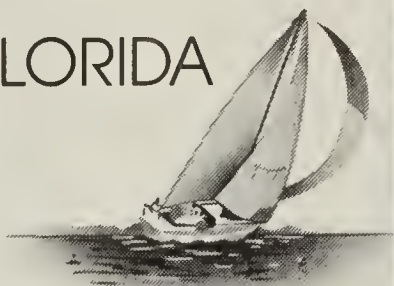
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*Lower initial doses of 120 mg may be warranted in patients who may have an increased response to verapamil (eg, the elderly or people of small stature). Total daily dosages above 240 mg should be administered in divided doses. Calan SR should be administered with food.

Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

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COMMENTARIES

Physician training in the recognition and reporting of child abuse, maltreatment, and neglect

Each year in the United States, more than 1% of all children are suspected of being the victims of child abuse, maltreatment, or neglect. There are approximately 1,200 substantiated cases per one million population annually. It is disturbing that 4,000 children die each year from physical abuse, and 10% of children under age five who are seen in emergency rooms are the victims of inflicted injuries. When abused children are returned home, 15% experience repeat abuse, and 10% of that number die.¹

Historically, New York State, as well as every other state, has attempted to increase the identification of abused children by passing legislation. These laws have made it mandatory for certain professionals, including physicians, to report cases of possible child abuse when these professionals, called "mandated reporters," have "reasonable cause" to suspect that abuse may have occurred. Professionals required to report suspected abuse include physicians, surgeons, medical examiners, coroners, dentists, osteopaths, optometrists, chiropractors, podiatrists, resident physicians, interns, registered nurses, Christian Science practitioners, day care center workers, foster care workers, child care workers, mental health professionals, psychologists, law enforcement officials, peace officers, police officers, hospital personnel, district attorneys, assistant district attorneys, social service workers, teachers, and school officials. There are specific criminal and civil penalties for the failure to report suspected abuse, and reporters are granted immunity from criminal and civil liability for reports made in "good faith." Despite this, studies show that physicians continue to have difficulty in identifying and reporting suspected child abuse.^{2,3}

In an attempt to further increase the identification of abused children, the New York State Legislature passed Chapter 544 of the Laws of 1988, establishing a new requirement for all physicians, chiropractors, dentists, registered nurses, podiatrists, optometrists, psychologists, dental hygienists, and others. On or after January 1, 1991, these mandated reporters must provide documentation of having completed two hours of specified course work re-

garding the identification and reporting of child abuse and neglect when initially applying for or renewing their professional license registration or limited permit. Those who applied for registration before January 1991 will not be required to meet this requirement until they reapply at a later date.

The statute also includes training requirements for certification or licensure of classroom teachers, school service personnel, administrators, and supervisors. All persons applying on or after January 1, 1991, for a provisional certificate or license valid for administrative or supervisory service from these disciplines must have completed the two hours of course work.

As developed by the New York State Education Department, the course materials meeting the requirements of Chapter 544 will be taught by instructors certified by the education department and must include information regarding the physical and behavioral indicators of child abuse and maltreatment.⁴ The learning objectives include defining what constitutes abuse, maltreatment and neglect; distinguishing among various behavioral and environmental characteristics of abusive parents or caretakers; identifying physical and behavioral indicators of physical abuse; identifying physical and behavioral indicators of maltreatment and neglect; contrasting the physical and behavioral indicators of sexual abuse; explaining the requirements, mechanisms, and legal protections and penalties for reporting or failing to report suspected abuse.

The completion of the two hours of training in child abuse identification is intended to be neither an exhaustive nor a complete review of this serious and complex issue. Rather, it is an initial attempt to increase the identification and reporting of possibly abused children among physicians and other mandated reporters.

Unfortunately, the courts tend to rely heavily on the existence of positive physical findings to help adjudicate whether physical and/or sexual abuse has taken place, despite all of the present data that seem to indicate that physical findings, especially in the prepubescent child, are

relatively less common. A delay in reporting may actually allow a healing of the signs of physical and/or sexual abuse that has taken place. It is obvious that the above findings can have serious repercussions for both the child and physician when a case of sexual abuse is not recognized and/or reported. Children who have been sexually abused are not usually victims of physical violence, but rather victims of physical and emotional misuse and betrayed trust. It naturally follows that clinical manifestations are therefore often variable and occasionally confusing. In cases of incest, this may present a severe emotional and economic crisis to the child and to the child's family. It is not uncommon that the victims are knowledgeable of the possible legal consequences which will interfere with reporting of the victims and seeking treatment of the offenders. In evaluating sexual and/or physical abuse, the physician is obligated to present accurate medical evidence to the court, or the results may be devastating both to the child and to the child's family. More often than not, the process of reporting and investigation by Child Protective Services is beneficial to the family unit.

While Chapter 544 places further requirements upon already overburdened physicians, it is apparent that all

mandated reporters must become familiar with the significant problems of both the abused and the abuser. This will undoubtedly require even more advanced training. Yet physicians are in a unique position among health care providers in that they can play a vital role for their patients in early recognition and reporting. This will help us to reduce the immediate and long term physical, behavioral, and emotional morbidity of child abuse, maltreatment, and neglect.

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Autoimmune paraneoplastic diseases of the nervous system

An increasing number of paraneoplastic disorders affecting the nervous system are now recognized.¹ Virtually every segment of the nervous system has an associated paraneoplastic disease, including the cerebral cortex, brainstem, cerebellum, spinal cord, peripheral nerve, myoneural junction, and muscle. Autoimmune mechanisms have been proposed for many of these diseases, and recent studies have concentrated on the identification of specific antigens that might be involved in the immune process.

Identification of the antigens involved is an important step in determining the nature of autoimmune disease. Once an antigen is identified, then it must be determined that an autoimmune response directed against that antigen is capable of reproducing the disease. With an autoimmune pathogenesis established, studies may then be directed towards the inciting factors that lead to the autoimmune response. As noted below, several antigens have now been linked to autoimmune paraneoplastic disease. A strong argument supporting an autoimmune pathogenesis has been made for one of these, the voltage-operated calcium channels of the neuromuscular junction.²

The Eaton-Lambert myasthenic syndrome is one of the best characterized of the neurologic paraneoplastic disorders. It has been associated with a number of tumors, most commonly small cell carcinoma of the lung. Antibodies from affected patients have been demonstrated to react with voltage-operated calcium channels on the presynaptic membrane. These channels are down-regulated in the presence of the antibody,³ and the resulting degree of inhi-

bition in calcium flux correlates with disease severity.² These calcium channels have been demonstrated in neurons as well as in cell lines derived from small cell lung carcinoma.⁴ Thus, antigens have been demonstrated and evidence of an autoimmune pathogenesis is accumulating.

Paraneoplastic cerebellar degeneration is now recognized to be associated with antibodies reacting with Purkinje cells.⁵ Two antigens have been identified: CDR62 and CDR34. Both antigens are expressed by Purkinje cells and CDR62 has also been found in tumor tissue.⁶

Antigens in peripheral nervous tissue have also been associated with autoimmune paraneoplastic disease. Anti-Hu antibodies react to neuronal nuclei and are found in subacute sensory neuronopathy.⁷ Antibody to myelin-associated glycoprotein is found in some paraneoplastic peripheral neuropathies.⁸ Anti-GM1 antibodies are found in motor and sensorimotor neuropathies due to plasma cell dyscrasias.⁹ Antibodies directed against a 23 Kd retinal protein (CAR antigen) are associated with cancer associated retinopathy.¹⁰

Myasthenia gravis is not a paraneoplastic process in most patients. However, approximately 10% of these patients have a thymoma and approximately 70% have hyperplasia of the thymus. The thymus contains myoid cells which can express the involved antigen, the acetylcholine receptor.¹¹

A number of other paraneoplastic neurologic syndromes are recognized, including brainstem encephalitis, limbic encephalitis, opsoclonus-myoclonus, necrotizing myelopathy, Guillain-Barré syndrome, motor neuron disease, mononeuritis multiplex, and dermatomyositis/poly-

myositis.¹ Many of these are suspected of being autoimmune diseases, and the search for the responsible antigens is underway.

Several broad factors determine immune reactivity. The "genetic environment" determines general immune reactivity as well as which antigens may be reactive in an individual. The "immune environment" is a balance of regulatory networks dictating the activity of the immune system as a whole as well as reactivity for specific antigens. The "antigenic environment" encompasses the antigen which is expressed on the surface of cells as well as local factors affecting the reaction of this antigen with immunologically active cells or antibodies. Finally, the "effector environment" determines the specific actions taken by the immune system such as antigen clearance, cell lysis, etc.

The autoantigens noted above are present in normal cells. In paraneoplastic disease, however, these same proteins are expressed in the markedly different environment of the tumor cell. Current theories have concentrated on local aberrations of the tumor environment and methods by which these aberrations allow the presentation to the immune system of a previously nonimmunogenic protein in a manner conducive to an autoimmune reaction. Factors in addition to the local tumor environment must also be considered, including the reactivity of the immune system as a whole.

Hematologic tumors provide a unique opportunity to study the relationships between antigen, antigen-presenting cells, and the immune environment. In this issue of the *Journal* Liesveld et al¹² describe a case of Eaton-Lambert myasthenic syndrome in a patient with a mixed nodular type of non-Hodgkin's lymphoma. A deficit of T cell regulation allowing the emergence of a B cell clone is suggested. Presumably this same deficit of T cell regulation could be a factor in allowing the autoimmune response. The occurrence of other cases of hematologic tumors associated with autoimmune disease suggests that a regulatory abnormality of the immune system may be a factor in autoimmune disease. Additional evidence of an underlying regulatory abnormality is the presence of multiple autoimmune processes in single patients.¹³ Antiacetylcholine receptor antibodies (and other autoantibodies) have been

found in approximately 25% of patients after bone marrow transplantation,¹³ a condition producing altered immune regulation.

The contributions of antigen, presenting cells, and immune regulatory state in the production of autoimmune disease may soon be clarified. Future cases of hematologic autoimmune paraneoplastic syndromes should be investigated for the presence of autoantigens in tumor as well as normal tissues. Studies of immune regulatory function should also be done. Such studies might determine whether an immune regulatory abnormality is sufficient to allow an autoimmune process, or whether changes of antigen or antigen presentation are also necessary.

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Percutaneous catheter drainage for acute empyema

Improved cure rate using CAT scan, fluoroscopy, and pigtail drainage catheters

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ABSTRACT. Percutaneously inserted pigtail nephrostomy catheters were used to treat empyemas in 12 patients. Thoracic computed tomographic (CT) scan and fluoroscopy were used to localize precisely and place the catheters into loculated collections of fluid. Percutaneous catheter drainage (PCD) of empyema was successful in seven of seven patients (100%) in whom standard tube thoracostomy (STT) had initially failed and in three of five patients (60%) who had PCD as the initial drainage procedure. Overall, PCD was successful in treating empyema in ten of 12 patients (83%). The procedure was well tolerated and there were no complications. PCD is a safe and effective method for drainage of loculated empyemas as the initial procedure or after STT has failed.

(NY State J Med 1991; 91:4-7)

Standard tube thoracostomy (STT) is often used as the initial drainage procedure in thoracic empyema. Unfortunately, failure of STT drainage of empyemas has been reported in 26% to 60% of patients, and these patients may require open surgical drainage procedures.¹⁻⁷ Some authors advocate early decortication for acute empyemas.⁸⁻¹² However, general anesthesia and major surgery may result in prolonged morbidity, mortality, and additional cost.¹³ We report our experience with 12 patients who were treated with percutaneous catheter drainage (PCD) for loculated empyema.

PATIENTS AND METHODS

The medical records of 12 consecutive patients who underwent PCD were reviewed. The following demographic, clinical, radiologic, and microbiologic information was collected: age, sex, predisposing factors, temperature, white blood cell (WBC) count, gross appearance of pleural fluid, pleural fluid cultures, pH, lactate dehydrogenase (LDH) level, glucose level, location of empyema, number of catheters used, and duration of catheter drainage. Empyema was defined as pleural fluid that was grossly purulent or which yielded positive cultures for bacterial pathogens. Additional criteria for PCD included pleural fluid with pH less than 7.0, glucose level less than 40 mg/dL or LDH level greater than 1,000 μ /L^{14,15} coupled with persistent fever, leukocytosis, and loculated effusion despite appropriate antibiotic coverage. Successful treatment was determined by reduction of fever, normal WBC

count, and roentgenographic resolution of the pleural effusion.

Frontal, lateral, and lateral decubitus chest radiographs were part of the initial evaluation of pneumonia and empyema. Patients with suspected loculated empyema had a thoracic CT scan for precise localization prior to percutaneous catheter placement.

Technique of Catheter Placement. Patients with empyema were premedicated with intravenous morphine and intramuscular diphenhydramine for analgesia and sedation. The patients were prepared with povidone-iodine and draped. After the empyema was localized under fluoroscopy, the site was anesthetized with local 2% lidocaine.

A 21-gauge Chiba needle was placed over the superior border of the rib into the empyema. The stylet of the needle was removed, and an 0.018 inch guide wire was placed through the needle. When the tip of the needle was within the pleural space, the guide wire could easily be advanced into the empyema cavity without any resistance or patient discomfort; coiling outlined the perimeter of the loculation. The track was dilated with a series of guide wire and catheter exchanges. Catheters were secured to the chest wall using 0 silk. We used 8.5 and 12 French cope loop type nephrostomy catheters, and 12 and 16 French ring McClean drainage catheters (Cook Inc, Bloomington, IN) (Fig 1). The pleural fluid was aspirated and sent for the following studies: pH, glucose, LDH, WBC, and bacterial cultures. When the diagnosis of bronchopleural fistula or multiseptated loculation was suspected, the radiocontrast agent Iohexol, 180 mg/mL diluted 1 to 1 with normal saline, was injected with fluoroscopic visualization.

A petroleum gauze dressing was placed over the puncture site to prevent air leak. The patients were monitored in the recovery room for one hour. The catheters were connected to a collection chamber to which a constant suction pressure was applied. The catheters were irrigated once daily with normal saline. Follow-up chest films and CT scans were obtained to determine catheter placement and empyema resolution. When the daily catheter output dropped below 50 mL of straw-colored fluid or 0 mL of purulent fluid, the catheter was removed (Fig 2).

RESULTS

Table I summarizes the demographic, roentgenographic, and CT findings. Of the 12 patients, eight were men and four were women. Their ages ranged from 21 to 75 years with a median of 32 years. Predisposing factors for empyema included eight patients with intravenous drug abuse (eight had serologic evidence of hepatitis B infection and four had thrush), and one patient with epilepsy and poor dentition. In one patient, empyema developed following STT drainage for hemothorax, and one patient was an elderly patient with diabetes mellitus.

The 12 patients treated for empyema were on antibiotics when the percutaneous catheters were inserted. There were eight positive pleural fluid cultures (Table II). In five patients, only one organism was isolated, and multiple organisms grew in three pleural fluid cul-

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FIGURE 1. Chest radiographs of a 25-year-old female intravenous drug abuser admitted with pneumonia and left sided empyema.

tures. In four patients, the pleural fluid was grossly purulent. All patients had persistent fever, leukocytosis, and loculated effusion in spite of receiving appropriate antibiotics for adequate duration. Six patients had right-sided empyema, five had left-sided empyema, and



FIGURE 2. Lateral chest radiograph obtained after initial catheter placement demonstrates a persistent loculation anteriorly.

there was one case of bilateral empyema. There were three patients with co-existing lung abscess.

In seven patients, STT did not adequately drain the empyema. CT scan revealed loculated effusion distant from the tube in six patients, and kinking of the tube in one patient. CT scan localized empyema in 12 patients, while lateral decubitus chest films demonstrated layering of free fluid in one patient. Seven patients required only one catheter, four patients with multiloculated empyema had two catheters, and one patient with bilateral empyema had one catheter placed on each side.

PCD was successful in ten patients. The duration of catheter drainage ranged from two to 30 days with a median of 6.5 days. Two patients underwent decortication. In one, decortication was done to remove thick pleural peel which prevented lung expansion, although pleural infection was controlled. Another patient was treated with early decortication four days after PCD was instituted, although he seemed to be responding to the treatment. One patient died of an unrelated cause 22 days after his empyema was successfully treated. Four patients required analgesics to treat pain at the catheter site. Two patients remained febrile after PCD. One patient's clinical course improved after he was switched to appropriate antibiotics following isolation of *Staphylococcus intermedius* in pleural fluid culture. Another patient had an undrained loculation which was treated successfully by placement of an additional catheter.

DISCUSSION

Catheters placed under fluoroscopic guidance led to successful treatment of empyema in ten of twelve patients. The patient population was young, with a median age of 32 and without any preexisting lung disease. In four of 12 patients, no organism was isolated from the pleural fluid, perhaps because of prior antibiotic therapy and/or failure to successfully culture anaerobes. The pleural fluid was grossly purulent in these four cases.

Fluoroscopic guidance of PCD succeeded in ten of 12 patients. Seven of 12 patients initially had STT, which

TABLE I. Clinical, Roentgenographic, and CAT Scan Findings

Patient No.	Age/Sex	Predisposing Factors	Roentgenographic Findings	CAT Scan Findings
1	24/F	Epilepsy; poor dentition	Right lower lobe infiltrate, loculated right pleural fluid, standard tube thoracostomy in position on frontal view	Right lower lobe infiltrate, loculated right lateral pleural fluid, standard tube thoracostomy misplaced posteromedial
2	37/M	Intravenous drug abuse	Right lower lobe infiltrate, right pleural fluid, standard tube thoracostomy misplaced	Right lower lobe infiltrate, right pleural fluid, standard tube thoracostomy misplaced
3	32/M	Intravenous drug abuse; alcoholism	Left lower lobe, lingular infiltrate, left pleural fluid, standard tube thoracostomy misplaced	Not done
4	25/M	Intravenous drug abuse	Massive right pleural fluid	Massive right pleural fluid, atelectasis right lung
5	75/M	Diabetes mellitus	Right lower lobe infiltrate, right pleural fluid	Right lower lobe infiltrate, two loculated right pleural fluid
6	26/F	Intravenous drug abuse	Bilateral cavitary infiltrate Loculated bilateral pleural fluid	Bilateral cavitary infiltrate Loculated bilateral pleural fluid
7	40/M	Intravenous drug abuse	Left lower lobe consolidation, loculated left apical pleural fluid, standard tube thoracostomy	Left lower lobe consolidation, loculated left apical pleural fluid, standard tube thoracostomy
8	34/M	Penetrating chest trauma	Two loculated right posterior pleural fluid collections, standard tube thoracostomy misplaced	Two loculated right posterior pleural fluid collections, standard tube thoracostomy misplaced
9	26/F	Intravenous drug abuse	Extensive left lung infiltrate, left pleural fluid	Extensive left lung infiltrate, left pleural fluid
10	21/M	Intravenous drug abuse	Left lower lobe infiltrate, left pleural fluid, standard tube thoracostomy kinked	Left lower lobe infiltrate, atelectasis, left pleural fluid, standard tube thoracostomy kinked
11	35/F	Intravenous drug abuse; alcoholism	Left lower lobe infiltrate, loculated left pleural fluid	Left lower lobe infiltrate, abscess, loculated left pleural fluid
12	49/M	None	Large loculated right pleural fluid	Large loculated right pleural fluid, right lower lobe consolidation

failed because of tube misplacement in six and kinking in one. These patients had had chest radiographs, and STT was done as a bedside procedure with repeat chest films following the procedure to confirm the position of the chest tube. Other workers have used similar techniques with favorable results. Van Sonnenberg et al¹⁶ used CT and ultrasound-guided PCD to treat successfully 15 of 17 patients after failure of STT. Westcott¹⁷ cured nine of 12

patients with empyema using fluoroscopically guided catheters, four of whom had failed to improve following conventional chest tube therapy. Crouch et al¹⁸ placed percutaneous catheters under fluoroscopic guidance, CT scan, and ultrasound to treat empyema, curing 14 of 20 patients.

STT failed because prior chest films did not clearly localize the fluid collection and differentiate pleural from

TABLE II. Pleural Fluid Characteristics, Microbiological Studies, and Patient Outcome

Patient No.	Pleural Fluid Appearance	Pleural Fluid Culture	Drainage Procedure	Patient Outcome
1	Grossly purulent	No growth	STT, PCD*	PCD successful
2	Yellow cloudy	No growth	STT, PCD	PCD successful
3	Grossly purulent	<i>S intermedius</i>	STT, PCD	PCD successful
4	Bloody	<i>S aureus</i>	PCD, decortication	PCD failed
5	Grossly purulent	No growth	PCD	PCD successful
6	Blood tinged; purulent	<i>S aureus</i> ; <i>E coli</i>	PCD	PCD successful
7	Serosanguinous	(1) <i>S viridans</i> (2) <i>Enterobacter aerogenes</i> (3) <i>Enterobacter cloacae</i> (4) <i>Enterococcus</i>	ST, PCD	PCD successful
8	Bloody	<i>S intermedius</i> <i>S epidermidis</i>	ST, PCD	PCD successful
9	Grossly purulent	<i>S viridans</i> <i>Streptococcus</i> <i>B. Melanogenicus</i>	PCD	PCD successful
10	Cloudy; serosanguinous	<i>Enterococcus cloacae</i>	STT, PCD	PCD successful
11	Yellow cloudy	<i>S aureus</i>	PCD	PCD successful
12	Thick green; purulent	No growth	PCD, decortication	PCD failed

* STT = standard tube thoracostomy; PCD = percutaneous catheter drainage.



FIGURE 3. Lateral chest radiograph and CT scan demonstrating cure following placement of a second catheter in the left cardiophrenic angle.

parenchymal disease,¹⁹ and because STT was done bedside as a blind procedure. In order to overcome these problems, CT scans were used in 11 patients who did not demonstrate free pleural fluid on decubitus films. CT scan identified the loculation and the number of fluid collections, and differentiated the fluid from consolidated lung and fibrotic peel. Fluoroscopic guidance permitted visualization of the catheters passing into the fluid collections.

Straight, rigid tubes used in STT are difficult to maneuver into certain areas such as the costophrenic and cardiophrenic angles without risking complications. The side hole of the straight chest tube is frequently blocked by a re-expanding lung, creating loculations at the costophrenic angles.²⁰ The use of soft, self-retaining catheters in PCD allowed easy access to these areas without risking injury. Post-catheter insertion, CT scan, and sinography confirmed correct placement. PCD was less traumatic and less painful than STT.

PCD was successful in three of five patients in whom it was done as the initial drainage procedure. Two patients underwent decortication. In one, decortication was done to remove thick pleural peel for lung expansion, though the empyema was completely drained. In another, decortication was done four days after the catheter insertion, although the patient seemed to be responding.

Percutaneous catheter drainage appears to be a safe and effective method in the treatment of loculated empyema, particularly in areas of difficult anatomical access. PCD should be considered when STT has failed, and in patients who are poor surgical candidates for decortication or other open drainage procedures. Whether PCD should replace STT for initial drainage of acute empyema should be evaluated by prospective randomized clinical trials.

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Eaton-Lambert syndrome

CASE PRESENTATION

Regina Fernandes, MD (Medical Intern): A 62-year-old man was admitted to the New York Infirmary-Beekman Downtown Hospital with polyuria, polydipsia, weakness, and edema of both legs over the preceding three weeks.

Seven months prior to admission, a chest film showed no abnormal findings. Three weeks prior to admission, the patient first noticed edema of both lower legs up to the knees, together with polyuria and polydipsia. On admission to a hospital in Florida, he was found to have hyperglycemia and hypokalemia; a chest film identified a mass in the upper portion of the right hilum, confirmed on computed tomographic (CT) scan. On the patient's immediate return to New York, his private physician treated him with NPH insulin, furosemide (Lasix), and potassium supplements. A repeat chest film confirmed the previously noted findings; liver function tests were said to be abnormal. The patient's symptoms persisted; the weakness now tended to interfere with his gait, and poor appetite contributed to a 25-lb weight loss over one month's time. The patient denied shortness of breath, fever, chest pain, hemoptysis, nausea, vomiting, or diarrhea.

His medical history included cigarette smoking, one pack per day for many years, and long-standing overuse of alcohol, which had been discontinued two months previously. He had had viral hepatitis 30 years previously. Diabetes mellitus, diagnosed two years before admission, was well controlled with glyburide (Micronase). The patient was allergic to penicillin. A review of systems was otherwise unremarkable.

Physical examination on admission disclosed a mildly cachectic man in no acute distress. His blood pressure was 120/80 mm Hg; pulse rate, 80/min; respiratory rate, 14/min; and temperature, 98°F. The skin showed only pigmentation attributed to solar exposure. Examinations of the head, eyes, ears, nose, and throat were negative. The neck was supple; there was no lymphadenopathy. The lungs were clear on auscultation and percussion. The heart sounds were normal; a grade I/VI systolic ejection murmur was audible over the left sternal border. The abdomen was flat, soft, and nontender, with active bowel sounds; the spleen and liver were not palpable. The rectal examination revealed no abnormalities, with a negative Guaiac test for blood on the stool specimen. The extremities showed bilateral proximal muscular atrophy of the thighs; two-plus pitting edema extended up to the knees bilaterally. There was no clubbing or cyanosis.

The neurologic examination revealed marked proximal muscle weakness in the lower extremities only. Orientation was intact; cranial nerve functions and deep tendon reflexes were normal.

The urine was cloudy, with a pH of 6 and specific gravity of 1.020, with large amounts of glucose and acetone; microscopic examination showed 2-4 white blood cells and 1-2 red blood cells per high power field. The hemoglobin was 14.7 g/dL; hematocrit, 41.8%; white blood cell count, 10,300/ μ L, with 70% mature polymorphonuclear leukocytes, 10% immature forms, and 20% lymphocytes. The platelet count was 113,000/ μ L; the prothrombin and partial thromboplastin times were within normal limits. The serum electrolyte levels were as follows: sodium, 141 milliosmols per liter; potassium, 2.2 millimole/L; chloride, 92 mmol/L; and bicarbonate, 16.1 mmol/L. The blood glucose was 377 mg/dL; blood urea nitrogen, 20 mg/dL; serum creatinine, 2.8 mg/ μ L; and serum magnesium, 1.4 mg/dL. The serum alkaline phosphatase was 448 units per liter (normal range, 13-39 U/L); total serum protein, 4.9 g/dL; serum albumin, 2.8 g/dL; bilirubin, 1.5 mg/dL; aspartate aminotransferase (AST/SGOT), 98 U/L (normal range, 7-27 U/L); alanine aminotransferase (ALT/SGPT), 86 U/L (normal range, 1-21 U/L); and lactate dehydrogenase (LDH), 1,726 U/L (normal range, 45-90 U/L).

The arterial blood gas determinations with the patient breathing room air indicated a pH of 7.49; PCO₂, 29 mm Hg; PO₂, 85 mm Hg; bicarbonate, 22 mm Hg; and oxygen saturation, 99%. The arterial-alveolar oxygen gradient was 25 mm Hg.

A chest film demonstrated the right hilar mass and haziness suggesting a left pleural effusion; the heart was normal in size (Fig 1).

The electrocardiogram (ECG) showed sinus tachycardia, with occasional auricular premature contractions. The T-waves were inverted in leads II, III, aVF, and V-3 through V-6; the ST segments were depressed in leads V-4 and V-5. Comparison with earlier ECGs showed no change.

Despite potassium supplements, the patient's serum potassium level remained low throughout his hospital course. CT scans confirmed the presence of a 3.0 × 1.5-cm right hilar mass (Fig 2), small bilateral pleural effusions, minimal ascites, thickening of the gastric wall, normal size of liver and spleen, and a 2-cm soft density in the left adrenal gland. An upper gastrointestinal series showed thickening of the mucosal folds in the fundus of the stomach. Bronchoscopy revealed the right upper lobe mass; biopsy and histologic study indicated the presence of a small-cell carcinoma. Evaluation of the patient's mus-

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FIGURE 1. Chest radiograph (posteranterior view) showing circumscribed right hilar mass (arrow).

cular weakness included an electromyogram, the results of which were characteristic of the Eaton-Lambert syndrome, suggesting a paraneoplastic syndrome. The morning serum cortisol level was 54 $\mu\text{g/dL}$ (normal range, 5–25 $\mu\text{g/dL}$); urinary excretion of free cortisol, 2,282 $\mu\text{g/24 hr}$ (normal range, 20–90 $\mu\text{g/24 hr}$); morning serum aldosterone, 3.4 pg/mL (normal range, 7–9 pg/mL). The serum hepatitis B surface antigen and antibody tests were nonreactive. The alpha-fetoprotein level was 0.9 nanograms/dL (normal range, undetectable in normal serum).

The oncology consultant recommended the initiation of chemotherapy as soon as possible. The patient, however, deteriorated mentally, with increasing lethargy. A CT scan of the brain and a lumbar puncture gave normal results, but shortly thereafter the patient refused to permit any further diagnostic or therapeutic efforts on his behalf. His lethargy and confusion increased; a follow-up chest film showed an increase in the left pleural effusion. Glycosuria and acetonuria persisted, despite improvement in the serum glucose level. Hypokalemic alkalosis, hypoalbuminemia, and abnormal liver function tests continued to be observed, together with a steady increase in the level of gamma glutamyl transpeptidase and in the total serum bilirubin.

By the end of his second week in the hospital, the patient

was extremely lethargic; at his family's insistence, chemotherapy was not initiated, and a do not resuscitate (DNR) order was written. The patient lapsed into a coma and died on the 21st hospital day.

Irwin Sharkey, MD (Chief of Medicine): Do you believe that this patient's persistent hypokalemia was due to the high cortisol levels associated with a paraneoplastic syndrome?

Dr Fernandes: Yes, in a patient with small-cell carcinoma and high serum levels of cortisol or a cortisol-like substance, a paraneoplastic syndrome is very likely, most commonly with hypokalemic metabolic alkalosis. In this patient, the hypokalemia was clearly made worse by the polyuria associated with decompensated diabetes mellitus.

Harold Coppersmith, MD (Attending Physician): Did you think his deteriorating mental condition was also related to the high cortisol levels?

Dr Fernandes: Yes, patients may show alterations in mental status from the effects of the opioid-like peptide fragments of the ectopically elaborated hormone. This patient experienced personality changes even before he was made aware of the pulmonary diagnosis.

George Braff, MD (Chief of Radiology): On representative films and CT scans of the chest, we can see the right hilar mass, well circumscribed (Figs 1, 2). With the chest film alone, it is difficult to evaluate the fluid at the lung bases, which is more readily demonstrated on the CT scan, more on the left than on the right. The left adrenal gland demonstrates the lesion as mentioned, which suggests a metastasis from the lung, rather than an adenoma; the right adrenal gland appears normal. A single thoracic spine view was obtained, and there appears to be some erosion of the fifth thoracic vertebra, consistent with a metastatic focus.

Dr Sharkey: Dr Blair, what did the bronchoscopy show?

Lester Blair, MD (Director of Pulmonary/Critical Care): There was an exophytic mass, which was occluding the anterior and apical segment of the right upper lobe. We had suspected small cell carcinoma from the beginning, based on his presentation with neurologic findings. He had no significant symptoms referable to the chest.

I had the opportunity to review the chest film that was taken six months before his admission here, and it was entirely normal, suggesting a subsequent rapid progression of his neoplasm.

Mary Chaglassian, MD (Medical Resident): In the differential diagnosis of this patient's illness, the two most important findings on admission were his profound hypokalemia refractory to treatment and the right hilar mass on radiographic studies. Of importance also were his history of long-standing cigarette smoking, uncontrolled diabetes mellitus, and abnormal liver function tests.

The most prominent features of hypokalemia and potassium depletion are neuromuscular. With this condition, a patient's complaints are usually muscle weakness, especially in the lower extremities; with severe or acute instances of hypokalemia, marked and generalized weakness of skeletal muscles may be prominent. Physical examination discloses the decreased muscle power and often decreased or absent deep tendon reflexes. The electrocardiogram commonly displays characteristic changes



FIGURE 2. Computed tomographic (CT) scan of lungs (representative cut) showing prominent right hilar mass (arrow).

with flattening and inversion of the T waves, increased prominence of the U waves, and sagging of the ST segments. Moderate potassium depletion rarely affects cardiac action, but when severe or rapid reduction of serum potassium occurs cardiac arrest may result. A variety of atrial and ventricular arrhythmias may be seen, especially when the patient is taking digoxin.

There are three principal causes of a decrease in serum potassium: gastrointestinal disorders or deficient dietary intake; increased renal excretion of potassium; and hypokalemia due to shift of the cation into cells without reduction in total body potassium.

Concerning the first of these three causes, the patient gave no history of vomiting, diarrhea, or loss of gastrointestinal secretions such as might occur with a villous adenoma, or after abdominal surgery with subsequent fistulae or uterosigmoidostomy. Diarrhea, when it occurs, may cause large potassium deficits, since potassium concentration of liquid stools is 40–60 mEq/L. This patient gave a history of decreased oral food intake.

As to the second cause, increased renal excretion of potassium leading to metabolic alkalosis, three pathophysiologic mechanisms may be involved. These are loss of gastric acid, contributing to metabolic alkalosis, which increases potassium concentration within the renal tubular cell; increased plasma bicarbonate concentration, which increases the delivery of fluids and bicarbonate to the distal nephron; and secondary hyperaldosteronism due to associated extracellular volume contraction, possibly contributing to continued high levels of potassium excretion in spite of potassium depletion.

This patient's arterial pH of 7.49 and 7.60 might have contributed to his low serum potassium levels. In addition, all diuretics except spironolactone, amiloride, and triamterene promote potassium depletion. In edematous patients with secondary aldosteronism, most diuretics can intensify the hypokalemia.

Hyperaldosteronism, either primary or secondary, can be a major cause of hypokalemia. Aldosterone is the most potent mineralocorticoid produced by the adrenal gland. It effects sodium reabsorption from the lumen of the distal tubules into the tubular cells, and in exchange both potassium and hydrogen ions enter the tubular lumen.

Primary aldosteronism is commonly due to an adenoma, most often unilateral, of the glomerulosa cells of the adrenal cortex; or more rarely, to an adrenal carcinoma or to bilateral adrenal hyperplasia. Hypersecretion of aldosterone can lead to elevation of serum sodium and chloride and to a decrease in serum potassium with alkalosis. The accompanying clinical manifestations include episodic weakness, paresthesias, transient paralyses, and tetany. Diastolic hypertension and hypokalemic nephropathy with polyuria and polydipsia are common. Personality disturbances, hyperglycemia, and glycosuria can also develop. Measurement of plasma renin is helpful in the diagnostic evaluation. Normal individuals will have a marked increase in renin in the upright position, while the patient with hyperaldosteronism will not.

The criteria for the diagnosis of primary aldosteronism are diastolic hypertension without edema; hyposecretion of renin, indicated by low plasma renin levels that do not increase appropriately during intravascular volume depletion,

or during upright posture, or with sodium depletion; and hypersecretion of aldosterone that fails to be reduced appropriately during intravascular volume expansion.

The secondary form of hyperaldosteronism due to aldosterone secreted by the adrenal cortex is designated secondary by stimuli originating outside the adrenal gland. It can mimic the primary condition and may develop in patients with hypertension and edematous conditions such as congestive heart failure, cirrhosis with ascites, and the nephrotic syndrome.

In the patient we are discussing, the minimal presence of ascitic fluid, the bilateral pleural and pericardial effusions as seen on the CT scans, and the bilateral leg edema would suggest the presence of secondary aldosteronism with high levels of plasma renin.

Other diseases that may lead to hypokalemia include renal tubular acidosis, monocytic or monomyelocytic leukemias, and Liddle's syndrome, a rare familial disorder in which renal potassium wasting is caused by an intrinsic renal tubular abnormality. Antibiotics such as carbenicillin, amphotericin B, and gentamicin can cause hypokalemia and renal damage. The patient here was not acidotic, did not have leukemia, and was not on antibiotic therapy.

Magnesium depletion can contribute to potassium depletion apparently due to increased renal and possibly gastrointestinal losses. This patient's serum magnesium level of 1.4 mEq/L (normal range, 1.5–2.0 mEq/L) could have also intensified his hypokalemic condition.

The third category of causes of hypokalemia is the shift of potassium into the cells without any depletion. Hypokalemic periodic paralysis, alkalosis, and insulin effect can contribute to such shifts. This patient gave no history of periodic paralysis in the past, and he was never treated with insulin for his hyperglycemia. However, his alkalosis, as we mentioned before, might have played a significant role in his hypokalemic condition.

Our initial approach to the differential diagnosis of this patient's illness concentrated on his profound electrolyte imbalance, with less attention to the significance of the right suprahilar mass. The latter was diagnosed at bronchoscopy as oat-cell carcinoma of the lung. Important other pertinent findings were his increased serum cortisol levels, the increased 24-hour urinary excretion of cortisol, the highly elevated alkaline phosphatase and gamma glutamyl transpeptidase levels, and the inhomogenous left adrenal gland on the CT scan. These findings, together with the profound hypokalemia, strongly indicated that a primary lung carcinoma of the oat-cell type, with metastatic lesion to the adrenal gland, was presenting with a paraneoplastic syndrome of ectopic ACTH secretion giving rise to Cushing's syndrome.

Small cell lung carcinoma accounts for 20–25% of all malignant pulmonary neoplasms. It is clinically and biologically distinct from the other three types of lung cancer, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Compared with the other cell types, small cell carcinoma has the most rapid doubling time and tends to present more often with metastatic disease outside the thorax. It is more often related to paraneoplastic endocrine syndromes such as Cushing's syndrome, or to the syndrome of inappropriate antidiuretic hormone (SIADH), as well as the neurologic myasthenic syndrome

of Eaton-Lambert.

Adrenocorticotrophic hormone (ACTH) from the pituitary and, consequently, cortisol are normally secreted in a cyclic rhythm, with maximal levels at about 8 AM to 9 AM, and minimal levels from 3 PM to 3 AM. Unless this on-and-off sequence is maintained, abnormalities in the metabolism of carbohydrate, protein, fat, and minerals ensue, ultimately giving rise to the clinical picture of Cushing's syndrome.

ACTH or ACTH-like substances, when secreted by tumors such as small cell cancer of the lung, do not enter the circulation in cyclic fashion, but are released more steadily throughout the 24 hours, producing paraneoplastic syndromes. The classic clinical features of Cushing's syndrome—plethora, obesity, striae, and hirsutism—appear only in those cancer patients who survive for a period of years. The clinical findings most commonly related to paraneoplastic secretions by lung cancer include dependent edema, pigmentation, weakness, and wasting of muscles, particularly of the limb girdles, leading to difficulty with standing, walking, and getting out of bed. Disturbances of mood may be prominent; drowsiness, confusion, depression, or frank psychosis occur to varying degrees. Hypertension is usually mild, and hyperglycemia without ketoacidosis may be present.

The clue to the diagnosis of this paraneoplastic complication of lung cancer is the finding of hypokalemia, defined as a plasma concentration of less than 3.3 mEq/L. It results from the excessive urinary and fecal loss of potassium, which occurs when plasma cortisol concentration exceeds 30 μ g/dL. In this patient, it was 64 μ g/dL.

With this paraneoplastic complication, the plasma corticotrophin concentration is consistently high throughout the 24 hours. The best means of diagnosing the syndrome is the dexamethasone suppression test, which causes suppression of ACTH release by the tumor and hence a reduction of cortisol secretion, with a pronounced overshoot of ACTH release when administration of dexamethasone is stopped.

The elevated level of serum cortisol in Cushing's syndrome that complicates lung cancer has an important effect on the tumor itself. Cortisol appears to hasten the spread of metastases, especially to the liver and brain; seemingly, it acts as a spreading agent for tumor cells. This emphasizes the importance of prompt diagnosis and therapy. The most effective treatment is removal of the tumor in the lung, but as we mentioned before, small cell lung cancer tends to present more often with metastatic disease outside the thorax. It has been shown to be more responsive to combination therapy in 70–90% of patients, and is also more commonly responsive to radiotherapy.¹

In addition, five-year follow-up data now suggest that small cell lung carcinoma is curable with combination chemotherapy. Therefore, it is important to identify and separate small cell lung cancer from the other types of non-small cell lung cancer for treatment purposes.

Randy Seewald, MD (Medical Resident): The Eaton-Lambert myasthenic syndrome (ELMS) is an autoimmune presynaptic disorder of neuromuscular transmission characterized by proximal muscle weakness and fatigue, often associated with small cell carcinoma of the lung.² This neurophysiological abnormality results from a de-

crease in the number of packets (quanta) of acetylcholine released from the presynaptic motor-nerve terminal in response to nerve impulses. The resulting weakness is myasthenic, that is, the patient complains of increased enfeeblement after exertion, but very often muscle power actually increases after brief exercise, a brief reversal of the myasthenic effect.

In myasthenia gravis, the muscular symptoms are secondary to an autoimmune process, whereby circulating antibodies against acetylcholine receptors lead to defective conduction at the myoneural junction. Although circulating antibodies against acetylcholine receptors are not found in the Eaton-Lambert syndrome, an IgG antibody, binding to nerve terminal determinants, may be responsible for the condition. The syndrome tends to improve with plasma exchange and after treatment with prednisone and azathioprine in cases of the syndrome not secondary to malignant neoplasms.

In contrast to true myasthenia gravis, the Eaton-Lambert syndrome is only slightly improved by treatment with neostigmine or pyridostigmine, though there may be a definite improvement in strength with the administration of edrophonium hydrochloride. However, the tendon reflexes in the Eaton-Lambert syndrome, unlike those in true myasthenia gravis, are almost always depressed or absent. Repetitive stimulation of motor nerves at tetanic rates in the ELMS syndrome usually causes a marked increase in the amplitude of the evoked muscle action potentials. Patients with the ELMS syndrome are extremely sensitive to decamethonium.

The ultrastructural changes at the motor end plates are characteristic for the Eaton-Lambert syndrome and differ from those seen in myasthenia gravis. Electron microscopy reveals a paucity and disorganization of presynaptic membrane-active zones and active-zone particles. These particles are topographically related to quantal release of acetylcholine and are thought to be the voltage-sensitive calcium channels of the presynaptic membrane. The serum IgG in ELMS may react with these voltage-dependent calcium channels, blocking their function, and thereby reducing the ingress of calcium into the nerve terminal. This phenomenon can account for the presynaptic impairment characteristic of this disorder.

Occasional cases with electrophysiologic features of both myasthenia gravis and ELMS occur; but in general the findings in each are distinctive. Tests of neuromuscular transmission are mandatory whenever this condition is suspected.

The male/female ratio in ELMS is approximately 1:1. Carcinoma is present in 72% of males and 32% of females, but is uncommon under the age of 40. More than 80% of the responsible tumors are small cell carcinomas. The syndrome may present up to three years before the tumor can be detected clinically. The prognosis for the tumor itself is remarkably favorable. Patient survival in the presence of ELMS averages four years, versus less than two years in its absence. The tumor mass is often remarkably small and may be discovered only at autopsy.

Small cell carcinoma expresses many neural antigens, which supports the view that it may be of neuroectodermal origin. Renewed interest in this disease reflects the growing evidence that autoimmune mechanisms may underlie

many of the paraneoplastic neurologic disorders that are associated with this tumor and less commonly with other neoplasms.

Patients with ELMS but without cancer have a significant increase over expected values in the frequency of the HLA B-8 and the HLA DR-3 histocompatibility alleles. Humoral immunity appears to play a major role in the pathogenesis of this syndrome and the presence of immunogenetic factors enhances the propensity to develop the syndrome in patients who do not have cancer. In one third of patients, the syndrome is not secondary to a neoplasm and may occur at any age.

ELMS is characterized by weakness and fatigueability of proximal limbs and torso muscles with relative sparing of extraocular and bulbar muscles. The lower limbs are more severely involved than the upper. With maximal voluntary contraction, the force produced by a weakened muscle increases for a few seconds and then again decreases. The tendon reflexes are hypoactive or absent in most patients. Autonomic manifestations occur, such as dry mouth, decreased sweating, orthostatic hypotension, and altered pupillary reflexes, in about 50% of patients.

The diagnosis of Eaton-Lambert syndrome depends on the characteristic clinical picture and on electrical tests of neuromuscular transmission. On electromyography, the amplitude of the compound muscle action potential evoked from rested muscle by a single nerve stimulus is abnormally small. Repetitive stimulation at 2 Hertz induces a further decrement, but stimulation at frequencies higher than 10 Hz or voluntary exercise for a brief period markedly facilitates the response, so that the evoked potential attains normal amplitude.

Tumor removal often brings about some measure of improvement from ELMS. Spontaneous remissions also occur in both tumor and nontumor cases. Administration of anticholinesterase medication has only a slightly beneficial effect. Guanidine hydrochloride, a drug that facilitates acetylcholine release, may give symptomatic relief of muscular weakness and fatigueability; this drug has no convincing effect on true myasthenia gravis. It is given orally in a total daily dose of 10–25 mg/kg of body weight, but toxic side effects, such as seizures and confusion, severely limit the value of this treatment. Plasmapheresis and immunosuppressant medications, such as prednisone and azathioprine, may be beneficial, in keeping with the proposed autoimmune nature of this disease.

Dr Blair: You mentioned that the ELMS may appear several years prior to any clinical evidence of the tumor. I am wondering if the Cushing's syndrome seen in this patient due to the tumor may have been manifesting itself for the past two years only as glucose intolerance and diabetes.

Dr Seewald: Yes, that is very possible.

Jay Liveson, MD (Director of Electromyography): At the conclusion of the electromyographic study of this patient, it appeared reasonably certain that he had oat cell carcinoma of the lung. The differential diagnosis here focuses on the muscle weakness. At first it is important to determine that the patient had genuine muscle weakness in spite of maximal effort. Then attention can be turned to localizing the problem to the specific part of the motor system. It can be a lesion of an upper motor neuron, brain

stem, or spinal cord, or a cortical lesion. Alternatively, it can be a lower motor neuron lesion in the anterior horn cells, nerve roots, peripheral nerves, neuromuscular junctions, or muscles.

At first, we reviewed this patient's history for clues. Several etiologies are suggested, including alcohol, which can produce a polyneuropathy; diabetes, which can affect the roots or peripheral nerves; the secretions of a hilar lung mass, which can interfere at the neuromuscular junction; and hypokalemia, which causes muscular weakness by an undetermined mechanism.

The history of proximal muscle weakness, borne out on the physical examination, suggests several causes. These include diabetic radiculopathy or neuropathy, or even polyneuropathy which sometimes affects the proximal muscles predominantly; a disorder at the neuromuscular junction; or a disorder within the muscle cells themselves.

Physical findings in addition include questionable extraocular muscle dysfunction, with some degree of ptosis and absent deep tendon reflexes. Proximal muscle weakness plus a pulmonary hilar mass makes the Eaton-Lambert myasthenic syndrome (ELMS) a consideration.^{3–5} The patient should be asked about dryness of the mouth, which this patient had experienced. This symptom occurs in more than 90% of patients with ELMS.

ELMS results from dysfunction at the neuromuscular junction, as Dr Seewald indicated. An abnormal presynaptic mechanism prevents the release of vesicles containing acetylcholine in adequate amounts when the presynaptic portion of the junction is stimulated by a nerve impulse. An anatomic correlate for this dysfunction is evident on electron microscopy.⁶ Clinically, a review of 50 cases of this syndrome² established that 100% of the patients had lower extremity weakness, slightly fewer had upper extremity weakness; 74% had dry mouth, 21% had ptosis, and deep tendon reflexes were depressed or absent in 90%.

How do we study such a patient with available electrodiagnostic tools? Only one finding can establish a myopathy. On needle electromyography (EMG), if we observe motor unit potentials (MUPs) that have low voltage and are of short duration, a muscle disease may be present. In all other conditions, the amplitude and duration of the MUPs are increased. In addition, on the EMG we look for evidence of abnormality at rest, such as fibrillation potentials, positive sharp waves, or complex repetitive discharges. All can occur in any lower motor neuron condition.

In this patient, we found that the EMG motor and sensory conduction studies were normal. The only abnormality was a slightly low amplitude of the evoked compound muscle action potential (CMAP).

Interestingly, some clues can be sought for ELMS during the physical examination. The patient is requested to exert the weakened muscles against a resistance. Then, shortly thereafter, a change is sought in the strength of those same muscles, or in the briskness of the deep tendon reflexes. In this patient, however, no changes were evident clinically.

In ELMS, every time the nerve potential fires down the neuron, an inadequate number of quanta of acetylcholine at the nerve ending is generated. If instead of single individual electrical potentials, you bombard the neuromus-

cular junction with many such potentials, you can mobilize more acetylcholine. The pathophysiology of this presynaptic abnormality is similar to botulism and hypermagnesemia. By contrast, in myasthenia gravis, the problem is postsynaptic; an adequate number of quanta of acetylcholine is being released, but the postsynaptic response is abnormal.

Myasthenia gravis and ELMS can be differentiated on the Jolly maximal stimulation test. Stimulation at 3/sec is the optimal test to demonstrate a decrement of the compound muscle action potential in both myasthenia gravis and in ELMS. To distinguish the two conditions, it is important, therefore, to request the patient to exert the muscle group being tested. For testing the hypothenar muscle group, the patient presses his fifth finger against a resistance; for the thenar muscles, the patient abducts the thumb. You then repeat the Jolly test at 3/sec. In the presence of ELMS, there may be as much as a four-fold increase (post-tetanic potentiation) in the amplitude of the compound muscle action potential, followed 90 seconds later by a marked reduction (post-tetanic exhaustion). This degree of post-tetanic potentiation does not occur in myasthenia gravis. The same post-tetanic potentiation can be demonstrated by high frequency stimulation, higher than 10/sec. This test is uncomfortable and is not routinely performed.

Another test of function of the myoneural junction is the measurement of "jitter."^{7,8} The terminal branches of a nerve innervate individual muscle fibers. When the anterior horn cell fires, all of these terminal branches are fired, but not precisely at the same instant. These slightly different intervals are summed up by the extracellular EMG electrode, resulting in a smooth compound muscle action potential curve. With the use of a special needle electrode, however, the firing of the individual fibers can be visualized separately on the oscilloscope. The intervals between the individual firings are relatively but not precisely constant, and it is this minor fluctuation that is called the "jitter." It reflects differences in the speed along the peripheral neurons and variations across the myoneural junctions. In the presence of any abnormality in the terminal twigs of the nerve, as with a polyneuropathy or at the neuromuscular junction in myasthenia gravis or in ELMS, for example, then the jitter is more pronounced.

In summary, this patient had a combination of recent onset of proximal lower extremity weakness, dryness of the mouth, absent deep tendon reflexes, and a hilar mass. On electrodiagnosis, the Eaton-Lambert myasthenic syndrome was demonstrated. ELMS is associated with lung tumors in 50% of cases. When a tumor is present, it is almost always an oat cell carcinoma. Only one of 25 tumors would be an adenocarcinoma. In this case, therefore, the histologic findings can be predicted with almost 100% certainty.

Dr Sharkey: There is a myopathy that is associated with endogenous steroid excess. What is the pathophysiology of that condition?

Dr Liveson: Steroids, especially fluorinated compounds, are known to cause symmetrical lower extremity weakness with prominent quadriceps atrophy. This condition reverses on discontinuing the steroids. Experimental studies have shown multiple metabolic changes that could ac-

count for such a myopathy. These include interference with oxidative metabolism⁹ and inhibition of protein synthesis.¹⁰ In some instances, the proximal lower extremity weakness may be related to vertebral collapse due to osteoporosis, with compression of nerve roots.¹¹ Probably some instances of such a neurogenic process have been mistakenly classified as "steroid myopathy."

Mitchell Raps, MD (Assistant Attending Neurologist): I was asked to see this patient after the diagnosis of the Eaton-Lambert syndrome was made. My involvement coincided with the patient's mental deterioration involving an acute psychotic episode with paranoid delusions. The question was whether he had a functional or an organic psychosis.

On the initial neurologic examination, as Dr Liveson mentioned, there was profound proximal weakness in the lower extremities, but I found some distal weakness as well. The deep tendon reflexes were absent. His mental status was markedly abnormal, with disorientation, dysarthria, poor memory, and paranoid ideation that other people were trying to poison him.

I had not seen the EMG and preferred to reserve judgment as to whether the Eaton-Lambert syndrome was truly present. I was concerned about the possibility of carcinomatous meningitis, neoplastic involvement of the cerebral hemispheres, and the possible presence of a cauda equina lesion due to metastatic disease in the spine. The CT scan of the brain was normal, and thereafter the lumbar puncture also was normal. I was convinced of the organic character of his mental state, and over the course of the next several days, that impression became clearly established.

The patient continued to be totally disoriented, claiming that he was in the basement of Beth Israel Hospital and had no idea of the date; his general condition continued to deteriorate. We could not do a bone scan. A normal result combined with the cerebrospinal fluid picture probably could have excluded significant spinal disease without myelography.

Because of the normal cerebrospinal fluid and the normal CT scan of the brain, I wondered whether we might be dealing with yet another paraneoplastic syndrome, namely the paraneoplastic encephalopathy that is well described in association with oat cell carcinoma and is characterized at autopsy by gliosis in the hippocampus bilaterally. That diagnosis cannot be made by CT scan of the brain or even by magnetic resonance imaging (MRI).

Of course there were other factors that might have contributed to the encephalopathy, in particular, his endocrine status and his hepatic status. Certainly the Eaton-Lambert syndrome alone would not involve the brain and could not account for the encephalopathy. The ptosis, which Dr Liveson quite correctly pointed out is not pathognomonic of the Eaton-Lambert syndrome, could as well have been a manifestation of carcinomatous meningitis. We were not able to obtain an electroencephalogram to determine what kind of electrical activity might be present in the brain; he was refusing both diagnostic and treatment measures.

This patient had a complex neurologic problem. As I indicated, the possibility of carcinomatous meningitis was high on the list of differential diagnoses, though the cere-

brospinal fluid did not bear it out. Had the patient lived longer, I would have repeated the lumbar puncture.

Jyming Wang, MD (Attending Oncologist): The most prominent feature on presentation was weakness. This patient had generalized weakness with pronounced proximal muscle weakness on admission. This led to a neurologic work-up, with EMG suggesting a diagnosis of the Eaton-Lambert syndrome. With an abnormal chest film, it was suspected that the patient had small cell lung cancer even before he underwent bronchoscopy. It is generally believed that patients with small cell lung cancer and Eaton-Lambert syndrome fare better than those without the syndrome. Unfortunately, the patient did not give us the opportunity to treat him and see how he would have responded.

Dr Sharkey: It is not common to see a patient with oat cell carcinoma with more than one manifestation of a paraneoplastic syndrome. This patient seems to have had three related syndromes: the Eaton-Lambert syndrome, Cushing's syndrome, and a syndrome causing a serious disturbance of his mental status.

Dr Wang: His proximal muscle weakness was very profound, and it appeared on admission that this could not be due to his electrolyte imbalance alone.

Olga Santiago, MD (Attending Endocrinologist): Unfortunately, the diagnostic tests necessary to confirm the cause of Cushing's syndrome was not done. To elucidate the cause of Cushing's syndrome, it is necessary to perform a dexamethasone suppression test. In this particular case a serum ACTH level would also have been useful, as ectopic secretion of the hormone is suggested by the patient's presentation. The elevated urine cortisol and plasma cortisol levels in this patient did confirm Cushing's syndrome, because of their sheer magnitude.

Arturo Constantiner, MD (Attending Nephrologist): Could the hypokalemia at the beginning have been in any way related to the diuretics he received?

Dr Sharkey: The patient was hypokalemic prior to his treatment with diuretics, which were given for only three days, and the hypokalemia persisted despite replacement therapy. Dr Santiago, do you see this type of hypokalemia in Cushing's syndrome?

Dr Santiago: When Cushing's syndrome results from an ectopic cause, the patient may show only biochemical abnormalities, with hyperglycemia and hypokalemic alkalosis; hypertension may be present, but the other physical characteristics of Cushing's syndrome often are not present.

FINAL DIAGNOSIS

Small cell carcinoma of the lung
Eaton-Lambert syndrome
Clinical findings suggestive of Cushing's syndrome and an encephalopathy.

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Physician involvement in capital punishment

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Although there were no executions in the United States for ten years until 1977, the debate over capital punishment continues to polarize society.¹ The apparent failure of law enforcement agencies to curb violent crime has resulted in a resurgence of support for the death penalty across the United States.² In New York State, for the past eight years, the assembly and the senate passed legislation reintroducing capital punishment, but the governor repeatedly vetoed the legislation. New York gave the nation the electric chair in 1890 and Nevada contributed the gas chamber in 1924—both on grounds of easing the prisoner's suffering.³

In 1976, the United States Supreme Court issued a decision upholding the constitutionality of capital punishment. The next year, Oklahoma and Texas were the first states to adopt lethal injection as a means of execution, followed shortly thereafter by Idaho and New Mexico. All four state medical societies acted to protect their members and declared that active physician participation in the administration of a lethal injection to execute a court-ordered capital punishment is ethically unacceptable. Other, more subtle, dilemmas, however, remained unresolved: Is it acceptable for the medical profession to loan its tools to the state for execution? How far can physicians go in giving indirect advice or assistance such as ordering the appropriate drugs from a pharmacy and still remain non-complicit?³

To those physicians who are in favor of or do not oppose the imposition of capital punishment, is it ethical to prepare and to administer or to supervise the preparation and administration of a lethal medication? Is it ethical for such a physician to make examinations during and after the lethal injection to determine whether the prisoner is dead? Should the physician participate to the extent of relieving acute suffering of the prisoner before or during the execution by lethal injection?

This essay takes no position on the societal-legal issue of the use of capital punishment in the criminal justice system. This essay is concerned with the physician's role or lack thereof in a society in which the criminal justice system includes capital punishment.

PHYSICIANS' VIOLATION OF MEDICAL ETHICS

Physician participation in torture and killing is abhorrent and should be universally condemned. The experience of the Nazi doctors and their active involvement in and supervision of the systematic extermination of millions of innocent human beings is probably the most reprehensible and unspeakable perpetuation of medical killing ever recorded in the history of mankind.

In 1975, the World Medical Association⁴ adopted the Declaration of Tokyo which states that a physician "shall not countenance, condone or participate in the practice of torture or other forms of cruel, inhuman or degrading procedures. . ." nor shall he "provide any premises, instruments, substances or knowledge to facilitate the practice of torture. . ." nor shall he be present during any procedure in which torture is used or threatened. The doctor's fundamental role, continues the Declaration of Tokyo, is "to alleviate the distress of his or her fellow men, and no motive whether personal, collective or political shall prevail against this higher purpose."

Yet, these restrictions have been violated in several countries such as Chile,⁵ Uruguay,⁶ South Africa,⁷ and the Soviet Union,⁷ where doctors have actively participated in torture and have falsified death certificates in order to conceal torture. Medical professionals are trained to heal but for various reasons, such as coercion or fear of reprisals, some physicians apply their knowledge and skills to inflict needless pain and suffering, design torture techniques, perform medical examinations on detainees before and after torture, and may even act as torturers themselves.

The heinous acts of medical experimentation and torture chronicled at the Nuremberg trials had a chilling effect on the world at large and the medical profession in particular. Lifton⁸ recounts in great detail the involvement of German physicians in the torture and killing of thousands of innocent human beings. The Nazis began with a program of sterilization and "euthanasia" under which German physicians actually carried out the murder of countless children and adults considered "unworthy of life," because they were physically or mentally ill, or socially undesirable, such as Jews, and climaxing with Auschwitz, where doctors performed selections, both on the ramp among arriving transports of prisoners and later in the camps and on the medical blocks.

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In Auschwitz, doctors supervised the killing in the gas chambers and decided when the victims were dead. Doctors ordered and supervised, and at times carried out, direct killing of debilitated patients on the medical blocks. At the same time, they kept up a pretense of medical legitimacy, signing false death certificates listing spurious illnesses. Doctors consulted actively on how best to keep selections running smoothly; on how many people to permit to remain alive to fill the slave-labor requirements of the I.G. Farben enterprise at Auschwitz; and on how to burn the enormous number of bodies that strained the facilities of the crematoria.

Then there was a radical escalation in both the vision and technology of mass murder at Auschwitz where Jews, Gypsies, and others were subjected to sterilization by injection, radiation, or surgery, to the injection of vaccines made from dental infections, to massive bleedings for blood-group experiments, to the use of human flesh for culture media and the making of lampshades and tobacco pouches, to brainwashing with chemicals, to deliberate infection with typhus, to the application of toxic substances to various parts of the body, to vivisections and to mass killings by phenol injections, gassing, shooting, and other cruel and inhumane methods.

These experiments and killings were only a small part of the role Nazi doctors played in Hitler's Final Solution. In fact, doctors supervised the entire killing process at Auschwitz from beginning to end. How were physicians, sworn by oath and conviction to ease suffering, transformed from healers to systematic killers?

The Nazi "biomedical vision" mass murder was committed in the name of healing the racially "diseased" body of the German republic. This destruction of the boundary line between healing and killing, Lifton argues, is at the heart of the Nazi enterprise. The Nazi doctors at Auschwitz underwent "an extraordinary individual-psychological shift from revulsion to acceptance." The schizophrenic situation for them lay in the "idea of doing constructive medical work within a slaughterhouse," thus explaining contradictions between murderous cruelty and momentary kindness which the Nazi doctors manifested in Auschwitz.

Yet nearly half a century after the Nazi holocaust, according to Amnesty International, the governments of approximately one third of the world's countries systematically practice or tacitly condone torture or ill-treatment to interrogate, punish, or intimidate political opponents.⁹ The techniques they use may include electric shock, prolonged beatings, sham executions, sensory and sleep deprivation, cigarette burns, water submersion, and mind-altering drugs. Physician participation in such torture should be condemned by all medical societies and medical organizations as well as the entire civilized world. Medical killing or "medicalized" killing as described above cannot be condoned under any circumstances. The Chilean College of Physicians and Surgeons is playing a leading role in denouncing doctors who participate in torture.¹⁰ The 1984 United Nations General Assembly adopted a "Convention against Torture." An international meeting on Doctors, Ethics and Torture was held in Copenhagen on August 23, 1986. The proceedings of that meeting and recommendations stemming therefrom have been pub-

lished.¹¹

The involvement of physicians even more than other persons in torture and medical killing is morally repugnant and socially, legally, and religiously unacceptable and totally unjustifiable.

PHYSICIAN INVOLVEMENT IN CAPITAL PUNISHMENT

In May 1977, Oklahoma became the first state to adopt lethal injection as a method of capital punishment because it is considered more humane than electrocution and because the cost is far less than the required repairs of the state's old electric chair, last used a decade earlier. Other objectives of lethal injection laws include the hope that more juries might be encouraged to vote the death penalty and the hope that such laws might be less apt to be struck down by the courts as "cruel and unusual punishment."¹²

Oklahoma requires the medical director of the Department of Corrections to order the drugs from a pharmacy near the state prison, and requires the physician who attends the execution to pronounce the prisoner dead, and to inspect the intravenous line inserted by the technician to insure proper flow of lethal drugs into the vein. One writer states the following:

the most compelling argument for physicians to oppose lethal injection, regardless of their beliefs about the broader issue of capital punishment is that no matter what safeguards are taken to assure that physicians will not directly have to perform the injection, the fact that lethal injection appropriates medical technology means that physicians inevitably will be involved at some point in the execution—whether by prescribing the lethal drugs, calculating the required dosage, or coaching the technician who inserts the catheter.³

In 1980, Curran and Casscells¹² reviewed the history of medical participation in state executions including guillotins, hangings, and electrocutions. These authors contend that the ethical principles of the medical profession worldwide should be interpreted to unconditionally condemn medical participation in this new form of capital punishment, ie, death by lethal intravenous injection. They suggest that such participation is a clear violation of the Hippocratic Oath whose language is very specific: "I will use treatment to help the sick according to my ability and judgment but never with a view to injury and wrongdoing. Neither will I administer a poison to anyone when asked to do so nor will I suggest such a course." They point out that unlike other methods, lethal drug injections require the direct application of biomedical knowledge and skills in a corruption and exploitation of the healing profession's role in society. They believe it is also ethically improper for physicians to monitor the condemned prisoner's condition during the drug administration and to pronounce his death when heartbeat and respirations cease. It is similar, say these authors, to the physician who examines a prisoner intermittently during torture or prolonged interrogation and pronounces him physically fit to continue his ordeal. They conclude that the United States medical profession should formally condemn all forms of medical participation in this method of capital punishment.¹²

Two years later, these same authors published an updated article on recent developments on doctors, the death

penalty, and lethal injections.² Several additional states passed new capital punishment laws, some authorizing lethal injection as a method of inducing death. The Oklahoma Corrections Department revised its procedures for execution, eliminating the role of the department's medical director in ordering the lethal drug or supervising the executions. Legal action was taken in the federal courts to prevent the use of prescription drugs for lethal injection. Prisoner groups filed suit against the Food and Drug Administration to force the outlawing of such uses because they violate drug licensing laws.

Sargent¹ discusses the difficult role of psychiatrists who practice in states that permit capital punishment and who may be pressed into evaluating or treating the condemned. He cites the famous *Ford v. Wainwright* ruling by the United States Supreme Court in June 1986. Ford was condemned to death for murder, but over the 11 years he spent on death row during exhaustive appeals he had become psychotic. Despite his psychosis, after a half-hour group evaluation, the governor's panel of psychiatrists found Ford "competent to be executed." The Supreme Court disagreed and established a constitutional right for mentally incompetent persons not to be executed. The American Psychiatric Association had filed an *amicus* brief criticizing, among other things, the adequacy of the evaluation process. Sargent concludes the following:

Psychiatrists should refrain from treating mentally ill prisoners on death row in order to restore their "competency to be executed." Such 'treatment' renders them double agents, in the service of the state as well as the prisoner. Participation in an act that will bring about a prisoner's death is expressly forbidden by the AMA Code of Ethics. It recalls the behavior of Nazi physicians, who used their professional skills not to heal but to kill.

On February 7, 1989, the American Bar Association's (ABA) House of Delegates adopted a resolution in which the ABA urges that no person with mental retardation, as now defined by the American Association on Mental Retardation, should be sentenced to death or executed, and states that the ABA supports enactment of legislation barring the execution of defendants with mental retardation.

The *Ford* case is also discussed by Thorburn,¹³ who points out that physician participation can occur in all phases of the death penalty, from trial to execution. Testimony, care of condemned persons, competency examinations, and physician witnessing of executions require medical decisions. That author feels that resolutions of medical professional associations against physician involvement in executions have not clearly identified and prohibited participation. The author concludes that physician participation in any phase of the death penalty is not permissible by medical ethical standards.

The prestigious *British Medical Journal*¹⁴ and *Lancet*¹⁵ devoted an editorial and letters, respectively, to the subject of doctors and the death penalty. The former publication urges doctors to articulate and implement ethical codes that unambiguously prohibit doctors from participating in executions and to widen the discussion to include the broader ethical issues of the death penalty. In April 1987, the Canadian Parliament began a controversial debate on capital punishment. One Canadian psychiatrist expressed his opposition to the death penalty:

If used in Canada, the death penalty will create many of the same ethical issues for physicians as it has in the United States, where citizens who were questionably mentally retarded or mentally ill have been executed, where psychiatrists are required to treat psychotic prisoners so they can become "fit for execution" and where physicians may be required to be present at executions.¹⁶

THE MORALITY OF THE DEATH PENALTY

The dilemmas for physicians and society concerning the death penalty continue to be debated and discussed.¹⁷ The morality of the death penalty per se is not directly addressed in this essay but cannot be totally avoided. An individual's position on capital punishment is the personal moral decision of the individual. The propriety of the death penalty is too real and alive an issue to abstain from its discussion. A moral judgment needs to be made about "whether some individuals are so costly to society, and so incorrigible, that their execution is society's only viable alternative."¹⁸

Some people argue that capital punishment is a deterrent to crime, and that by deterring crime, lives are spared and the quality of life enhanced.¹⁹ Conversely, some people believe that capital punishment is nothing more than useless vengeance and retribution.²⁰ Other opponents of capital punishment point to the occasional miscarriages of justice in potentially capital cases.²¹ Life imprisonment without parole is one alternative being proposed to replace legal executions in the United States.

MEDICAL ETHICAL PRINCIPLES

Various professional bodies have considered the issue of physician participation in or supervision of legally authorized executions. The condemnation by the World Medical Association of physician involvement in torture has already been mentioned earlier in this essay.

In 1980, the Judicial Council of the American Medical Association concluded that the fundamental concept of *primum non nocere* (above all, do no harm) bars medical participation in causing death by lethal drug injection regardless of the physician's personal view on the moral acceptability of capital punishment.²² However, the council found no ethical objection to a physician examining the executed person and declaring death. In 1986, the AMA upheld its position when it published the following statement on capital punishment:

An individual's position on capital punishment is the personal moral decision of the individual. A physician, as a member of a profession dedicated to preserving life when there is the hope of doing so, should not be a participant in a legally authorized execution. A physician may make a determination or certification of death as currently provided by law in any situation.²³

In 1980, the American Psychiatric Association stated that, "The physician's serving the state as executioner, either directly or indirectly, is a perversion of medical ethics and of his or her role as a healer and comforter." In 1981, the World Medical Association passed a resolution condemning physician participation in capital punishment, stating that "it is unethical for physicians to participate in capital punishment, although this does not preclude physicians certifying death."²⁴ In 1986, the medical associations of the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) passed a resolution declaring it in-

defensible for any physician to participate in any act connected to and necessary for the administration of capital punishment.²⁴ They further stated that, "For a physician to prepare, administer or monitor any procedure with a view to injuring a human being or to train others to do so would be a perversion and corruption of medical knowledge and skill and of the physician's responsibility to and role in society." In its *Ethics Manual*, the American College of Physicians clearly states that "Participation by physicians in the execution of prisoners is unethical."²⁵

OPPOSING VIEWS

Although most physicians and organized medical societies and organizations are opposed to physician participation in capital punishment, some physicians disagree and genuinely feel that they should do whatever is in the best interest of their patient, ie, the condemned prisoner. One physician who supports the concept that a doctor should give the lethal injection states that "when doctors decide not to participate in capital punishment and let a medical technician give the injection, they are breaching their responsibilities to the patient."²⁶

Physicians have the responsibility to ensure that their patient receives proper care and a quick merciful death. If a life must be taken, it should be taken in the most humane way possible. That does not necessarily mean that physicians support executions, however. All the medical profession requires in the context of capital punishment is that "the choice be based on the individual physician's judgment, reached after careful reflection, that the chosen course is best designed to minimize the harm done to society."¹⁹

Some members of the legal profession argue that "the medical profession's policy of opposition [to lethal injections] cannot withstand the scrutiny of rational analysis which inexorably leads to the conclusion that physicians are obligated to perform the injections."²⁷ These lawyers contend that no matter what its stand on capital punishment per se, the medical profession has a moral duty to help society provide a painless method of death for legally condemned persons and to prove that vengeance alone is not the ultimate aim. Such opinions notwithstanding, the overwhelming view of doctors and medical associations is that "physician participation in any phase of the death penalty from trial to execution, is not permissible by medical ethical standards."¹³

POLICY STATEMENT OF THE MEDICAL SOCIETY OF THE STATE OF NEW YORK

The Committee on Bioethical Issues of the Medical Society of the State of New York (MSSNY) believes that the use of capital punishment in the criminal justice system is a societal-legal issue, not a medical one. The following statement, adopted by the Council of the MSSNY on May 10, 1990, takes no position on that issue but is concerned solely with the role of the physician in a society in which the criminal justice system includes capital punishment. The statement is consistent with and is intended to be supportive of the Principles of Medical Ethics of the American Medical Association.

A physician, as a healer and a member of a profession dedicated

to the preservation of life, should not be a participant in a legally authorized execution but may certify the death of the executed person on the grounds that this does not constitute active participation in the execution.

Participation in an execution is deemed to include, among other things: 1) the determination of mental and physical fitness for execution; 2) the rendering of technical advice regarding execution; 3) the prescription, preparation, administration, or supervision of doses of drugs in jurisdictions where lethal injection is used as a method of execution; and 4) the performance of medical examinations during the execution to determine whether or not the prisoner is dead.

Participation in a legally authorized execution is *not* deemed to include the following actions and, accordingly, a physician *may act* in any of the following ways: 1) to serve as a witness in a criminal trial prior to the rendering of a verdict to determine guilt or innocence of an accused person; 2) relieve acute suffering of a convicted prisoner while he is awaiting execution; 3) certify death, *provided that* the prisoner has been declared dead by someone else;* and 4) perform an autopsy following an execution.

This statement is firmly rooted in the principle that a physician's first consideration is to do no harm: *Primum non nocere*.

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* This proviso assures that the physician will not be in the position of determining *whether* death has occurred, since a determination that death has not occurred would make the physician a participant in the execution—for example, by establishing that additional electric voltage is necessary to assure death.

The Great War: Its impact on the British and American medical communities, 1914-1918

JOHN S. HALLER, JR, PhD

INITIAL MEDICAL RESPONSE

With the outbreak of war in August 1914, thousands of physicians and surgeons left private practice to serve their respective armies. This migration to military service did not come without significant impact on personal lives and on the profession itself. Across the British Isles and its overseas dominions, medical men responded to England's appeal for civilian surgeons to supplement the work of those in the service. In addition, senior students from medical schools volunteered for positions as dressers. In Toronto alone, 61 Fellows of the Academy of Medicine joined the Army Medical Service for the First Contingent, Clearing Hospital, and University of Toronto Base Hospital. From the medical student body of Toronto University, six officers and 88 men went into service from among the undergraduates, while 252 volunteered from the graduate body of the Faculty of Medicine. In addition, physicians from Australia, New Zealand, South Africa, India, and Canada gave additional assistance in the form of hospital equipment and auxiliary personnel, and many offered their homes as convalescent stations for invalid soldiers and sailors.¹(pp157-158)

Fifteen months into the war, Charles M. Benson, MD, in his presidential address to the Dublin University Biological Association, remarked that a total of 42,378 physicians and surgeons had registered with the United Kingdom's Medical Register. Soon after the outbreak of the war, the licensing bodies provided supplemental examinations in order that students might qualify more quickly for commissions in the Naval and Army Medical Services. As a result, the number of senior students qualifying for commissions in the military increased measurably in 1915. However, since many students in their second, third, or fourth year of medical school received combatant commissions or became surgeon probationers, the number of candidates presenting themselves in 1916 declined by nearly a fourth. What represented a bare sufficiency of men entering medical schools during peacetime became a marked deficiency, presenting an alarming crisis during the subsequent years of the Great War. Many of those men who had intended to enter medical school found the

call to arms a greater attraction, fearing that they would not qualify for service before the war ended.²(pp86-87)

One immediate effect was a larger proportion of women students matriculating in medical schools. At the London School of Medicine for Women, for example, a record 110 women entered in 1914, compared with 69 the previous year, and an average of 44 for the three preceding years. Similar ratios applied at Guy's, King's College, St Mary's, and Cambridge, where the numbers of entering male students declined from previous years. According to one observer, the war had "given women an opportunity of proving their mettle, and that they have taken it with earnest enthusiasm is common knowledge."²(pp88-89) He concluded that the war had levelled many prejudices, "and not least among them is that against the women members of our profession."²(pp88-89)

Another early impact of the war was in the establishment of medical reciprocity between Great Britain and its overseas dominions. "This became necessary," noted W. H. B. Atkins in his presidential address before the Academy of Medicine in Toronto in August 1914, "on account of the necessity for those holding the license of the College of Physicians and Surgeons of Ontario to go with the Canadian Contingents to Great Britain and France, and therefore to work under the auspices of the War Office."¹(p161)

Notwithstanding the increased numbers of women in orthodox medical schools and the establishment of medical reciprocity, practitioners such as osteopaths, chiropractors, homeopaths, and Christian Scientists (known later to medical orthodoxy as the "Bolsheviki of Medicine"), sought recognition during this period, intending to capitalize on the call for civilian doctors. The scarcity of medical personnel gave these practitioners the opportunity to secure a place alongside orthodox medicine. In some instances, especially in the United States, the efforts proved successful. California, for example, admitted osteopaths as interns in state hospitals and osteopaths became members of the medical examining boards in Texas, California, and Washington.³(p25)

Not all practitioners expressed satisfaction with this loosening of restraints. Although homeopathic physicians had sought and were admitted to the US Army and Navy Medical Reserve Corps, they complained bitterly that their "special branch of training [was] not recognized and given free and fair trial in treating the sick in our Army

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Hospitals." Homeopaths were particularly scornful of the seeming lack of interest by orthodox medical schools in the materia medica. Too much time, they argued, had been given to laboratory techniques such as microscopy, chemistry, bacteriology, physiology, pathology, and anatomy, and too little time to an understanding of drug therapy. One particularly scornful homeopath accused the medical profession and state boards of medical examiners and licensure in the United States of "drug nihilism" in their lack of concern for the materia medica.⁴(pp270-271)

Another early byproduct of the war was the realization by the British medical profession of its dependence on Germany for synthetic drugs, analgesics, antipyretics, alkaloids, salicylates, and potash salts. The monopoly in Germany of the manufacture of these valuable drugs, originally produced in Britain, resulted in the temporary resurrection of older remedies from the aging materia medica.

Yet another byproduct was the interruption in the exchange of information by the postponement of numerous meetings of medical and scientific societies. The International Medical Congress, scheduled to meet in Munich in 1917, was suspended in 1915 in the belief that the hatred generated by the war would not have diminished by that time. Indicative, too, was the announcement by German scientists in 1915 that they intended to remove medical works of English, French, and Russian origin and replace them with "purely German medical nomenclature." The Allied attitude was just as spiteful, with physician Atkins remarking that German medical science had become overly developed at the expense of the more humane side of medicine. He accused German intellectuals, including many scientists and medical doctors, of discrediting themselves and German science by misunderstanding the causes of the war. "Can we ever trust the German scientists again?" Atkins queried.¹(pp159-160)

EPIDEMIOLOGY

When the consequences of war bring together large numbers of men from various geographical areas of a single country, or multiple countries, sanitarians face the problem of attempting to contain epidemic diseases brought to the camps from different localities. With the constant ingress of soldiers from every part of the globe to man the trenches in France, the menace of contagious diseases became the center of attention for hygienists, sanitary personnel, medical doctors, and scientists. Not only did these personnel focus their interest on the incubator nature of trench warfare, they also worried about the return to their respective homelands of troops who had become carriers for these diseases.⁵(pp74-77) Randolph Hudson, MD, of Denver, Colorado, remarked in 1915 that when historians eventually recorded the grim carnage of the war, they would also have to show the astounding sanitary precautions taken to ensure the health of the fighting soldier. From the physician's standpoint, the war had become an immensely important arena in which statistics on various diseases could be secured on a scale never before obtained. Medical prophylaxis, which had become the watchword of medicine, could be assessed using hundreds of thousands of men situated in comparatively similar environments.⁶(pp378-379) According to A. G. Butler, compil-

er of *The Australian Army Medical Services in the War of 1914-1918*,² "The effect of the war on the science of preventive medicine is chiefly discerned not in accretions to factual knowledge or in the discerning of new principles, but in its influence on the intellectual attitudes and outlook of its generation. It encouraged insistence upon reality: in particular, insistence that preventive medicine shall be based upon exact knowledge of the origin of the various disorders that resulted in 'wastage,' military or natural, or, ultimately in national responsibility for the payment of a war-pension for disease due to or aggravated by war service."⁷(vol 2,pp483-484)

Nevertheless, the failure to address some of the epidemic diseases lies, in part, with the state of the medical corps at the outbreak of the war. Even though medical personnel understood the principles of epidemiology, the need for assembling huge armies meant the near impossibility of applying many accepted medical principles. As a result, physicians and sanitarians found themselves with the unenviable task of directing much of their attention toward the treatment and care of the sick rather than toward prevention. The numbers of men required for service in the armies simply precluded focusing on more prophylactic measures. Thus, contagious diseases such as measles, meningitis, pneumonia, scarlet fever, and influenza thrived under army methods of assembly, travel, and housing. "We have not been able to control those diseases spread by the secretions of the respiratory tract," remarked Mazyck P. Ravenel, MD, a professor of preventive medicine at the University of Missouri. "In this fact lies the greatest weakness of the Army defense against disease and death by disease."⁸(pp29-30)

Sanitarians found the close quarters of men in camp life an ideal environment for disease transmission. Men who had not been exposed to diseases in their own regions were particularly vulnerable. For example, soldiers from the American South were susceptible to acute respiratory infections. Adding to this situation were the complications created by overcrowded camps and insufficient blankets and clothing for the men. Within this environment, the ravages of disease, particularly those of a respiratory nature, took their inevitable toll. In the Crimean War, the French had lost 75,000 men to disease and only 10,240 to battle wounds. Similar statistics existed for the American Civil War, and again in the Spanish American War, in which disease proved 14 times more deadly than wounds incurred in battle.⁸(p22) Within the American Army in the Great War, 41,000 soldiers died of pneumonia, 2,000 of meningitis, roughly the same number of tuberculosis, and 3,000 of diseases such as diphtheria, scarlet fever, typhoid fever, dysentery, smallpox, and malaria. At Camp Sherman near the Appalachians, the death rate from influenza in the fall of 1918 was surpassed only by the plague in London in 1665 when 14% of London's population died in a seven-month period.⁹(p233)

A young man entering the army had a much greater danger of illness than his counterpart in civilian life. To minimize this danger, Ravenel urged prohibitions against the habit of "promiscuous spitting" and recommended the elimination of the large-room barrack. He recognized, however, that other aspects of camp life, including mess halls, theatres, and areas for religious worship, continued

to offer a dangerous environment, especially for young men who grew up in rural areas and who were particularly susceptible to measles, mumps, scarlet fever, and the pneumonias.^{8(p30)}

Despite the discovery by Jenner in 1796 of the first vaccine, rendering harmless one of the great menaces to armies in past wars, smallpox remained a problem in the war zone of Galicia with its largely unvaccinated civilian population.^{10(p5)} Measles incapacitated large numbers of men; its side effects, especially pneumonia, carried a mortality rate which ran as high as 45%. As a result, measles proved to be one of the more serious diseases of the Great War.^{8(p25)}

Like measles, mumps prevailed in most army camps and its significance lay principally in the amount of lost time it took from the duties of soldiers. Moreover, its long incubation period made it difficult to isolate. In two camps in the United States scarlet fever assumed near epidemic proportions. Cases of diphtheria occurred in only seven camps as of July 1918, and in no camp did it reach epidemic proportions. Epidemic cerebrospinal meningitis, 45 times more prevalent in army than in civilian life, had the highest mortality of all the epidemic diseases. In some camps, such as Pike and Beauregard, physicians and sanitarians sprayed throats of known carriers with a solution of di-chloramin T. Not until 1918 were arrangements completed for the provision of anti-endotoxic meningococcus serum, prepared at Cambridge and the Lister Institute for the treatment of cerebrospinal fever.^{8(pp26-27)}

By 1917, neither cholera nor typhus had reached the western theatre, although it remained a decided factor on the Serbian front, in Montenegro, Galicia, and the Balkan states. Nonetheless, the danger of introducing these diseases among healthy troops remained a fear for all sanitarians who well understood the problems of moving large bodies of troops from east to west without proper quarantine and customary disinfection. Although the military losses from typhus did not compare with earlier wars, the aggregate number of deaths among both the civilian and military populations was exceedingly large.^{11(p29)}

Typhoid fever is an infectious and communicable disease caused by the germ typhoid bacillus, which becomes active when introduced into the alimentary canal. Most commonly transmitted by infected water, milk, shellfish, and flies, the bacteria became a grave danger to massed troops. In previous wars, nearly every fifth man serving in the army contracted typhoid fever.^{12(p145)} In order to staunch this epidemic flow, Sir Almroth Wright in 1898 inoculated 4,000 Indian Army troops with typhoid bacilli. In Wright's book, *A Short Treatise on Anti-Typhoid Inoculation*, published in 1904, he recounted the extensive trials carried out during the South African war when 14,628 men volunteered for inoculation. Unfortunately, the records of inoculation were lost and the statistical studies carried out after the war understandably proved unreliable. Of the 328,244 British troops engaged in the Boer war, there were 57,684 cases of typhoid, or one in six of the troops engaged, with 8,022 deaths.^{13,14(pp37-38)}

Although Wright had a difficult time justifying his theory to the British medical community, American sanitarians proved less obstinate. Major Frederick F. Russell of the United States vaccinated troops on a voluntary basis

in 1908 and later repeated the effort in 1911 in San Antonio, Texas. Of the 12,801 men inoculated, only two developed typhoid. Russell's success, compared with the statistical evidence of typhoid at other camps, convinced medical and military administrators of the need for mandatory anti-typhoid vaccination in the military services. In 1898, for example, a similar camp at Jacksonville which held 10,759 soldiers reported 1,729 cases of typhoid with 248 deaths.^{15(p230)}

Russell gave soldiers three injections of the typhoid germ in a watery suspension. Later, during the Mexican border affair, American troops were inoculated separately for the para-typhoids A and B. By August 1917, men were receiving the para-typhoids A and B combined with the typhoid as a triple vaccine. A year later, doctors replaced this with a lipo-vaccine which combined in oil the typhoid and para-typhoids into a single injection. This method reduced considerably the time and effort required to give six separate injections. Although American soldiers benefited from the vaccine, typhoid and the para-typhoids were not completely eradicated since many of Europe's soldiers went to war without the vaccine; moreover, in France in July 1918, there was evidence that not all American soldiers had received the vaccine.^{8(p24)} Nevertheless, the mortality rate for typhoid fever, which amounted to 14.83% per 1,000 of the US Army in 1898, accounted for only 0.08% per 1,000 among the expeditionary forces in 1918. The antityphoid inoculations introduced into the army and in national sanitation efforts between 1900 and 1915 resulted in a precipitous decline in deaths from this cause.^{16(p126)}

Unfortunately, the results recorded earlier by Major Russell in American army camps did not convince British and French authorities to require similar vaccination. At best, their record of vaccination was spotty, and voluntary rather than mandatory.^{15(p230)} Wright, who was convinced of its effectiveness, pleaded for compulsory inoculation in a long letter to the London *Times*, explaining the risk of infection and urging the Army to follow what armies in other countries had made compulsory. Lord Kitchener, who knew well the experience of typhoid fever in the South African War and in India, responded by ordering every soldier sent abroad to be inoculated against typhoid. Even so, some 20,000 British soldiers suffered from typhoid and 1,100 died from it.^{17(p37)} Had Wright not made this effort, the number of deaths from typhoid might have reached as many as 125,000 men in the British army alone.^{14(p42)} Not surprisingly, 305 of the 421 cases of typhoid fever in the British Army in 1915 were of uninoculated men, 35 of whom died. Even with these unfortunate cases, the situation had markedly changed from the earlier South African campaign, in which the number of deaths from typhoid exceeded the total number of men killed in action. In contrast, the numbers of typhoid cases in the Great War were comparatively few and deaths were rare among those receiving vaccination.^{6(p379)}

NEW THEORIES AND TECHNIQUES

Although the war diverted scientific energies from their normal applications, creative thought and original scientific research did continue, even though they were focused in more narrow fields of interest. Evidence of this activity

occurred in any number of critical areas, including the study of war psychoses, burn treatment, and war surgery.

From the earliest days of the war, stories had come in from the western front of strange new diseases originating in the stress and horrors of modern warfare. "After making all possible allowances for exaggeration and highly colored lay reports of technical and medical matters," commented the authors of *The Medical Department of the United States Army in the World War, Vol X, Neuropsychiatry* (1929), "it became apparent that some new medical problems has arisen in connection with the reactions of the central nervous system to the new conditions of warfare." It also became apparent that this new type of illness could undermine the manpower of modern armies because of soldiers' inability to withstand certain types of high explosives.^{18(p1)}

A new grouping of injuries, known variously as "battle shock," "nerve shock," "shell fright," "gas fright," "war neuroses," "mental shock," "wounds of consciousness," "neurasthenia," and "nerve fatigue," became increasingly prominent among the wounded in the trenches. The effects of shells constantly bursting above the trenches included such unexpected results as loss of memory, blindness or dimness of vision, loss of taste and smell, impaired hearing, and various physical and mental complaints. There were cases of staring eyes, violent tremors, cold extremities, and looks of terror. Even though not actually hit by shrapnel or other flying projectiles, and although from all outward manner unaffected by shell fire, troops were dazed by the continual concussions of artillery above the trench line. Physicians were divided over whether the causes were mainly physical or mental. Some, for example, were inclined to look for injuries of the central nervous system, blaming the affections on the bursting power of the shells and the resulting molecular changes in the brain and fluids produced by the detonations. Others emphasized psychological factors similar to those found in civilian practice. Almost all agreed, however, on the importance of the constitutional makeup of the individual exposed to shell fire as an important contributing cause. During and after the war, the medical literature on this phenomenon seemed to have no bounds, challenging as it did many contemporary theories associated with the civilian malaise known as neurasthenia.^{19-24,25(p65)}

The treatment of burns underwent a similarly substantive change during the war as physicians made significant advances with the use of paraffin wax. Barthe de Sandfordt first drew attention to the use of paraffin wax treatment for burns in 1903 in China. His formula, which later sold under the name Ambrine, remained a proprietary secret. Nevertheless, doctors tested paraffin wax extensively during the war and introduced several substitutes for the proprietary Ambrine. Some preparations were made by dissolving in a paraffin base such antiseptics as acriflavine, brilliant green, dichloramine-T, and eucalyptus oil. Colonel Hull, RAMC, devised one of the more popular substitutes known as No. 7—a mixture of neutral paraffin wax containing small amounts of olive oil, vaseline, oil of eucalyptus, and Bnaphthal. The wax acted to seal the burned area from air, forming a protective dressing in which the burned area could heal. In some cases, surgeons first placed a layer of liquid petrolatum over the burn, fol-

lowed by a layer of absorbent, and then a cover of paraffin. In either method, medical personnel changed the applications every 24 hours to remove the lymph collected under the wax shell, followed by a mild cleansing of the area, drying of the wound, and the application of another dressing.^{26(pp192-193),27}

One of the outstanding features of the Great War was the recognized value of blood transfusion in cases of extreme hemorrhage. Although not a new concept, its popularization in the war saved many lives. In the early days of the war, the only recourse was the injection of a saline solution which remained in the blood stream but a short time. Although saline worked in a crisis, it provided no permanent effect. Bayliss's gum saline provided some additional time for surgeons but offered little help for the badly hemorrhaging patient. In 1920, at the Fifth International Congress of Surgery, Depage and Govaerts presented clinical findings on those conditions in which patients failed to respond to saline solutions. These included cases in which the systolic blood pressure fell below 80 mm Hg, and showed no signs of recovery, and in which the red cell count fell below 4,000,000 in six hours from the commencement of bleeding.^{28(p1133),29(p197-206),30}

The Great War also ushered in a plethora of challenges for military surgeons who, hampered by the wartime impediments to aseptic conditions and the unavoidable rush during periods of intense fighting, found themselves often operating without mature consideration of actual circumstances. Wounds caused by shrapnel predominated among the hospital cases, followed by wounds caused by machine-guns, grenades, infantry rifles, and large projectiles.^{31(p54)}

Prior to the Great War, the ratio of those killed in warfare to the number wounded approximated 1 to 4 and was determined to a considerable degree by the mode of fighting. With the exception of the American Expeditionary Forces, for which the ratio was about 1 to 4.2, the number killed constituted an appreciable share of the total casualties. For the French, the ratio was 1 to 3; for the British armies, the ratio was 1 to 2.9; while the German Army had a ratio on the western front of 1 to 2.8. Most military strategists recognized that trench warfare tended to increase the ratio of killed to wounded.^{29(p50)}

As a result of trench warfare, surgeons discovered a higher percentage of bullet and shrapnel wounds of the face among the fighting soldiers. The two distinct types were embedded and piercing shots, and tangential or groove shots. Both resulted in serious infection. Typical were situations in which the teeth (including crowns, pieces of bridge, and foreign debris) were driven into the tongue, or teeth were driven into the floor of the mouth and throat. When hit by a bullet or shrapnel, the teeth themselves became missiles driving into the body. And in those instances in which teeth were abscessed or otherwise infected, they carried life endangering bacteria into the wounded tissue. Such wounds bled profusely, but could be checked with proper packing and compression. Where arteries were tied off, secondary hemorrhage was rare unless there was serious infection owing to septic mouth, abscessed tooth, or complicated dental problems. When the mouth became infected, from whatever reason, the area of the face experienced capillary blood clots and widespread

sepsis. The fact that many young soldiers were reaching molar impaction age tended to complicate wounds of the jaw. Inflammations from a molar, "stirred into activity" as a result of a fracture of the jaw, required all the skills a surgeon could muster. A bullet or other projectile that sheared off a half dozen teeth, leaving live nerves exposed, usually forced the surgeon to extract the teeth rather than perform a root canal, since surgery often had to be accomplished under the handicap of a broken jaw or wounded face. Surgeons found that the presence of necrosed roots near the region of a fracture, or septic teeth, served to deter a union of bones. For this reason, surgeons typically removed all teeth in the line of fracture to ensure the success in a bone graft.^{32(pp1183-1185)}

The surgery of the Great War was chiefly the surgery of infected wounds. This was totally unlike what physicians had expected, since innovations in first aid methods, iodine disinfection, better fixation of the wound, and transportation improvements were thought to have reduced the causes of infection to a negligible degree. However, ordinary first aid and external disinfection failed miserably to accomplish the expected results. The reasons for this failure lay in trench warfare, the increased use of artillery, and the resulting nature of shrapnel wounds, trauma, and infection which took place almost simultaneously with the injury. In addition to the common pyogenic organisms, surgeons faced the prospect of deadly tetanus and gas bacillus infection. With the use of prophylactic injections of antitetanic serum, physicians drastically reduced the incidence of tetanus. Infection by the gas bacillus was a more serious problem and one which neither vaccine nor serum seemed to influence. Infection was prompted by lacerated and contused wounds caused by high-explosive fragments that penetrated muscle tissue, or by wounds which cut off arterial supply. For many unfortunates, amputation became the only recourse once a localized gas infection became deep and malignant with gangrene.^{29(pp265-289)}

Surgeons distinguished between several categories of wounds: ricochets, embedded shots, and piercing shots. With the lower velocity firearms of former times, projectiles often simply pushed the blood vessels away. However, the high velocity firearms of the Great War penetrated even the smallest arteries. As a result, surgeons faced the added burden of dealing with an increased number of artery lesions. At short range, bones and joints shattered into a number of fragments and, at long range, were easily penetrated by high velocity weaponry. To complicate matters, corpsmen found it nearly impossible to properly dress wounds on the firing line because of the dirt, mud, and trench water. Infections due to common pyogenic organisms, tetanus, and gas bacillus were common products of this trench environment.^{31(p54)} Because of cultivation over hundreds of years, the tetanus organism was endemic to the soil and a deadly ally to the scratch, bullet wound, or shrapnel injury. Without the protective dose of antitetanic serum given immediately following the injury, there was no guarantee of immunity.^{33(p102)}

The beneficial influences of the war on surgery were principally in the popularization of existing procedures. These included blood transfusion, the use of nitrous oxide and oxygen anesthesia, bone and nerve surgery, and orthopedic constructive work. Other methods that were reintroduced

included secondary suture of wounds, the excision of wounds and primary suture, and the ligation of the bleeding point to arrest hemorrhage. New discoveries consisted of bismuth-iodoform-paraffin-paste to combat infection, Dakin's solution of chlorinated soda, the solution of acetate of aluminum, flavine or tryptaflavin, hypertonic salt solutions, the Carrel drop method using rubber tubes inserted along the whole length of the wound (Figs 1, 2), Ambrine, and the use of calipers for extension in cases of fracture.^{28(p1134)}

Theodore C. Janeway, Professor of Medicine at Johns Hopkins University, noted in an address before the Alpha Chapter Maryland of Phi Beta Kappa in 1917 that the "essential gifts of war to medicine are unparalleled opportunity for experiment and the most powerful stimulus to utilize that opportunity to the full." Although animal experimentation continued to be an essential part of medical discovery, the tragic but extraordinary circumstance of war provided the opportunity for duplicating conditions essential to biological experimentation and permitting the study of experimental results based on a large number of cases. War, which Pirogoff defined as "a traumatic epidemic," and which Hippocrates recognized as "the only proper school for the surgeon," gave to surgery the best possible experimental laboratory. On the battlefield, surgeons from the Greeks onward treated fractures and dislocations, managed wounds, practiced asepsis and antisepsis, attempted amputations, and learned to control hemorrhage and infection, the two most important elements in the structure of modern surgery.^{15(p216)}

Typical of the attitude of military medicine and surgery was that of James Krauss, in a paper read before the ninth

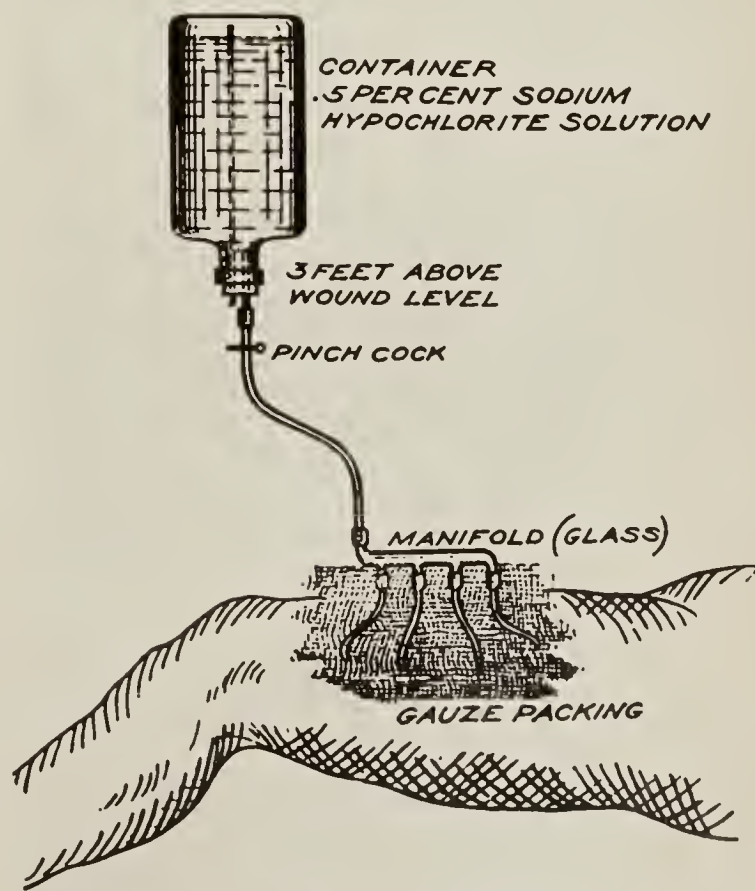


FIGURE 1. The Carrel-Dakin method of wound irrigation (reprinted from Arthur WH: Carrel's method of wound sterilization. *Milit Surg* 1917; 40:495).



FIGURE 2. Nurse adjusting flow of liquid to wound (reprinted from Loewy G: Carrel's method of treatment of infected wounds. *NY Med J* 1917; 106:799).

annual meeting of the American Association of Clinical Research in Boston on September 15, 1917:

There is nothing in military medicine and surgery that does not belong to civil medicine and surgery. There is nothing in the arrangement of hospitals, bases and units, in the field, nothing in the treatment of the wounded and diseased in action, that is different from hospitals and treatments given in a civil life; nothing in the methods of sanitation practiced in military life respecting food, water, conservation of life and energy, personal habits and the prevention of diseases that is not vital in civil sanitation: except the fact that overwhelming masses of men are collected in certain limited areas and consequently the administration of therapeutic and sanitary measures when needed must be inordinately rapid. Military medicine and surgery and sanitation, in this war as in any other war, are emergency medicine and surgery and sanitation en masse.^{34(p298)}

For Krauss and Janeway, knowledge acquired from the war could never have been obtained in ordinary times. Indeed, the war left an enormous plethora of material for observation, examination, analysis, experiment, correlation, and synthesis. It provided a mass of data on hereditary influences and on the environment and, as some physicians hoped, an ample data base for better knowledge of the principles and practices of medicine and surgery.^{34(p306)}

Notwithstanding this paean to military medicine and

surgery, physician B. C. Keister of Roanoke, Virginia, challenged the belief that war served as a catalyst for advancing science and medicine. "While I am fully aware that war experience in medicine and surgery is a great teacher along many lines," he observed, "yet, without the careful study and painstaking laboratory work in our great scientific schools in times of peace, there could be but little real progress in medical science." While recognizing war's beneficial impact on emergency surgery, he felt it had nevertheless impeded the work of scientists and laboratory workers moving tediously to improve medical science.^{9(p234)}

Although surgeons returning from the war were usually anxious to adapt procedures learned from medical surgery, they were also aware that war surgery had its limitations in affecting change in civilian surgery. For one thing, until wounded, soldiers were usually exceptionally fit, while in civilian practice, those requiring surgery were often impaired to some degree by their disease and its duration. Also, in war, surgeons did not have extended periods of time in which to exercise judgment; the conditions of battle, the physical fitness of the soldier, and the nature of the injury simplified the options and reduced the importance of preoperative judgment available to the surgeon. In contrast, the physical condition of the patient and his recuperative powers in civilian surgery were factors that often contraindicated a serious operation and the patient's chances of recovery. Similar contrasts applied to pathology, which differed markedly between civilian and military medical practice. In military medicine, pathology tended to be more precise simply because the range of injury was more defined, including its causation and effects. In civilian medicine, the range of pathology was far more extensive owing to the varying ages and degrees of physical fitness of patients and the nature of their diseases.

The same held true for prognosis and treatment which, for military doctors, seemed more definite due to the relative youth of the soldier, his physical fitness prior to injury, and the usually clear indications of damage created by the wound, its gross damage, and infection. Surgeons in the war theatre were often rushed by the events around them to perform their surgery quickly, without any operative scheme worked out in advance. In civilian surgery, this process was typically more extended, with nonoperative measures weighing just as heavily as operative indications. Charles F. M. Saint, professor of surgery at the University of Capetown, South Africa, noted the following:

In warfare, when everything was judged from the army standpoint, the limits of surgery, especially in rush periods, were in great measure determined by necessity of production of the maximum of benefit to the greatest number of wounded; in civil practice the individual is all important, and surgery is employed to produce the maximum benefit to the individual. In general terms war surgery, especially in forward areas at busy times, is that of injury of the multitude, whereas civil surgery is that of disease of the individual. The assessment therefore, of the influence of war on modern surgery is by no means straightforward or easy; it is apt to be greatly exaggerated by those whose only surgical experience is that of war, but it may be considerably underestimated by those who saw none of it. At the same time, surgery of front areas was in many respects a different problem from that of the base, where it tended to resemble much more closely similar surgery in civil practice.^{28(p1131)}

Thus, good judgment in civilian practice, if based on war experience alone, did not necessarily lead to the right choice of diagnosis and treatment. Moreover, according to Saint, the fundamental principles of surgery had not been affected by the war. Instead, it was the practice of surgery which bore its distinctive imprint. "The chief effects of the war," he wrote, "are seen in connexion with the art of surgery, mostly taking the form of new or modified methods of treatment."²⁸(p41)

In January 1920, Burton James Lee, MD, of New York, reported the findings of a questionnaire which he sent to the members of the New York Surgical Society asking for assistance in identifying war surgical methods that proved beneficial to civilian practice. In general, Lee wanted to ascertain whether the theory and practice of civilian surgery had acquired anything of importance from war zone surgery. The specific questions asked in the questionnaire included the following:

1. To what extent do you practice primary closure of compound fractures of extremities? Do you approve the principle?
2. To what extent do you use the principle of secondary closure of soft-tissue wounds? Do you approve the principle?
3. To what extent do you use the Carrel-Dakin solution and technic? Do you approve the principle?
4. To what extent do you use the principle of immediate active mobilization in post-operative joint conditions? Do you approve the principle?
5. To what extent do you use the principle of active mobilization of septic joints? Do you approve the principle?³⁵(p758)

In their responses, Lee found that the majority favored primary closure of compound fractures of the extremities except in cases of major wound contamination, extensive muscle injury, or when considerable time had elapsed between the time of initial injury and treatment. Most believed that careful debridement of the soiled and devitalized tissues was essential to primary closure. Several admitted to using the Carrel-Dakin wound treatment, followed by a delayed primary (six to eight days) or secondary (beyond eight days) suture. Lee discovered near unanimity in favor of secondary suture of soft tissue wounds when doctors had a thorough grounding in the Carrel-Dakin technique. "As one who has witnessed the transition from antiseptic to aseptic surgery twenty-five to thirty years ago," wrote one respondent, "I regard the demonstration of the fact that septic wounds can be sterilized without damage to the tissues, as the greatest contribution to surgery that the war has made. I do not understand why many able surgeons do not recognize the new principle involved in the Carrel-Dakin treatment." Interestingly, two hospital services responding to the questionnaire reported that they had abandoned the Carrel-Dakin procedure because of the inability to overcome the technical difficulties in maintaining adequate apparatus and solution. Nevertheless, from the responses received, it was evident that the members of the New York Surgical Society strongly supported the Carrel-Dakin method for wound sterilization, arguing that it was perhaps "the best contribution of the war to civil surgery" and that hospitals "must provide apparatus and accurately make solutions, and the surgeons must insist upon faultless technic"³⁵(pp759-760).³⁶ (Fig 3).

In response to the question on the use of immediate ac-

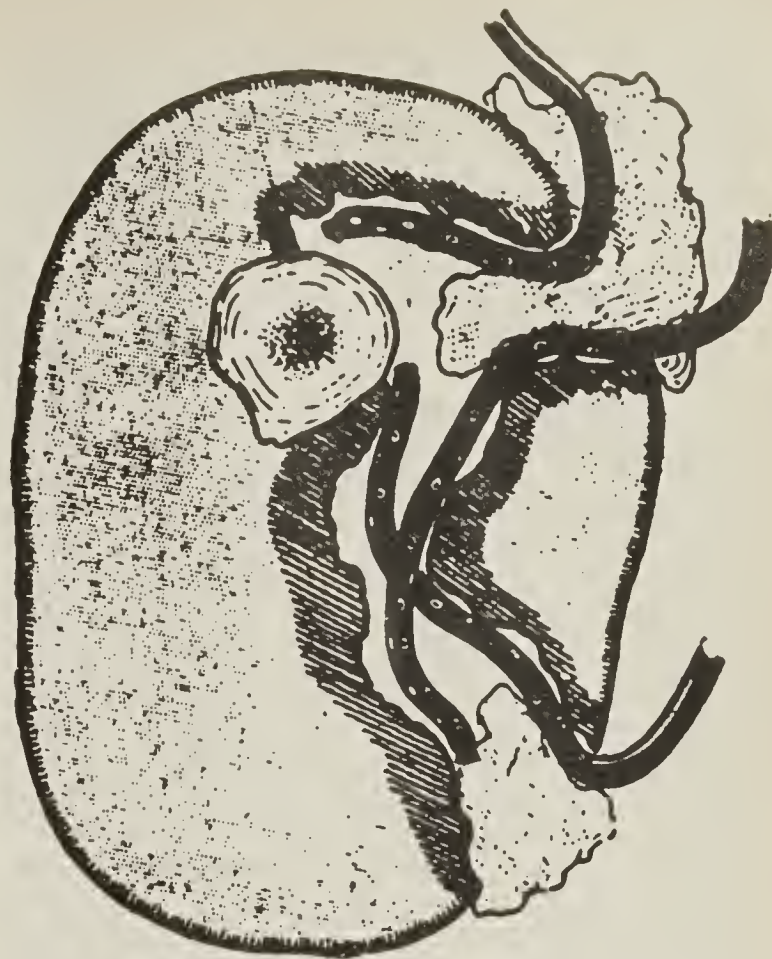


FIGURE 3. Illustration of Carrel's treatment of comminuted fracture and perforating wound. Two tubes are placed in the anterior wound and one in the posterior wound, and kept in place by gauze stuffed in the orifice (reprinted from Lowey G: Carrel's method of treatment of infected wounds. *NY Med J* 1917; 106:800).

tive mobilization in postoperative clean joint operations, surgeons acquainted with Willem's joint surgery found the practice of active mobilization fully applicable to civilian practice. As a result, Lee advocated immediate active motion within the first six postoperative hours and urged that dressings over the joint be kept loose and no larger than necessary to ensure wound protection and allow for drainage absorption.³⁵(p761) With respect to the principle of active mobilization in septic joints, most surgeons were "aghast and will not or cannot believe" that active mobilization applied equally to suppurating joints. "To my mind," wrote one respondent, "to move an active suppurating joint is to add insult to injury. Drainage, rest, and proper local treatment seem to be imperative." Lee, on the other hand, agreed with Willem that drainage of a septic joint was only possible by movement. "Active motion," he observed, "will really give the best possible drainage, while immobilization, drainage tubes, and irrigation cannot accomplish this result."

I have seen many men with suppurating knees walking about the wards of La Panne with normal knee-joints as regards function and perfectly painless joints, with a thin stream of pus running through the dressings covering their joint wounds and down their legs. These cases were impressive and absolutely convincing. The method is sound, and the experience in practicing it has furnished the proof. It represents a distinct advance in the treatment of septic joints, and it is thoroughly applicable to civil surgery.³⁵(p762)

Lee concluded his inquiry into the war's contribution to

civil practice by noting that the membership of the New York Surgical Society had given "thoughtful assimilation and application" of techniques and practices adopted during war zone surgery and that this new knowledge had contributed much to the theory and practice of civilian surgery.^{35(p762)}

THE ISSUE OF PHYSICIAN RIGHTS

The matter of individual prerogative in private practice vs generalized treatment for military officers became a matter of considerable concern for Sir Almroth Wright during the course of the war. In a lecture to the Medical Society of the Army in Boulogne, he insisted on the importance of standardized treatment in war medicine. Wright was an outspoken individualist yet, in time of war, he argued for army medical officers to sacrifice their professional freedom in the interest of encouraging more consistent medical care for the sick and wounded. In civilian practice, the individual practitioner could maintain independent charge of his cases, or he was free to follow whatever treatment appealed to him. In other words, the civilian practitioner could exercise private judgment except in those cases in which he chose the advice of a consultant. In most circumstances, the civilian doctor practiced on cases with which he was familiar and accepted new science as it filtered into his practice. The military surgeon, on the other hand, found his experience quite different. Confronting unfamiliar projectile wounds and wound infections, he was forced to take immediate action, with little opportunity to delay judgment or decision-making. Even more significantly, the military surgeon seldom had the opportunity to see the results of his work from start to finish, to learn whether the treatment was right or wrong. War zone hospitals had become little more than clearing hospitals from which cases, if fit to travel, were immediately sent to base hospitals in the rear. "There are thus lacking in the military hospitals in France," he observed, "all those provisos and safeguards which alone can make successful a system in which each medical man is a guide to himself."^{14(pp95-96)}

In order to make the work of the medical officer as effective as possible, Wright urged a change in the organization of the Medical Service which would depart from the principle of freedom in treatment and provide instead that "all treatment shall be regulated by orders and instructions."

These are, as you see, very big issues. It is a question of a conflict between our cherished professional tradition that every medical man must be quite unfettered in his choice of treatment; and the very foundation principle of the Army, that every man shall work, not as he individually thinks best, but as part and parcel of a great machine. . . . We have only to consider what has been achieved in this war by anti-typhoid inoculation, and the preventive injection of antitetanus serum; and to compare the brilliant results of these measures, enjoined as they are by direct instructions from Headquarters, with the results which would have been obtained if their carrying out had been committed to the individual judgment of medical men who had not had before the war any opportunity of convincing themselves by personal experience of the utility of either anti-tetanus or anti-typhoid inoculation.^{14(p97)}

Wright believed his proposed change would require bringing the work of medical officers to the highest stan-

dard and to coordinate their work from one hospital to another. Moreover, reformed medical treatment would require having an advising committee responsible for synthesizing clinical experience and discovering what results the various therapeutic procedures had obtained; and finally, determining on the basis of those inquiries the general instructions for treatment of different categories of cases. Wright urged the War Office to create a Medical Intelligence and Investigation Department composed of the best scientists and physicians. This body would have the responsibility for considering the various opinions put forward on the treatment of wounds, arranging the necessary clinical and laboratory investigations, and resolving any differences. The department also would have responsibility for focusing on new medical problems (trench foot, gas poisoning, trench fever, etc) and directing medical officers to specific forms of treatment.^{14(pp97-98)}

POST-WAR RESPONSIBILITIES

Doctors who served in the war and who reflected on its long term outcomes urged rigorous examination of soldiers returning from Europe. It was on the laboratory worker, hygienist, and parasitologist that the work of postwar reconstruction depended. Diseases common to Africa and the Orient had been imported into France, and soldiers from England and America, who had come in contact with these troops, threatened to bring the diseases back to their home countries after the war. D. Rivas of the Laboratory of Comparative Pathology and Tropical Medicine at the University of Pennsylvania urged a campaign of prophylaxis among the returning troops to protect the home population (and future generations) from chronic bacterial and parasitic diseases such as leprosy, malaria, filariasis, ankylostomiasis, schistosomiasis, and similar afflictions.^{5(p77)}

Rivas also urged the establishment of a commission which would look into the need for organizing sanitary camps and other facilities for the study of these diseases to prevent importation of the diseases into the United States. Rivas also recommended the building of quarantine stations on islands in the Atlantic "where every soldier and officer, without exception, should be submitted to a careful observation and study. . . before entering the country."^{5(p78)} In the end, preparedness meant not only fitting troops for combat, but, when the war was over, safeguarding the health of the home populations. Health agencies had a definite place in postwar reconstruction although they might not actually be incorporated within military agencies.

While Rivas indicated his concern for the returning soldier, others expressed concern with the numbers of males who demonstrated some physical defect and were thus unfit for military service. Specifically, they referred to cases of hernia and varicocele, and of defective teeth, adenoids, and tonsils. To correct this national problem, physicians and health officials urged a careful medical examination of all children, indexing any physical or mental defects. Statistics of young men in the United States were little different from those of other countries. Of 5,719,152 men examined, 1,680,175 or 29.35% were declared unfit for military duty because of some physical defect. A number of these defects could have been remedied in their inci-

piency.^{8(p31)}

Corrective actions recommended by physicians to reduce the numbers of military rejects included better care of babies and children, closer supervision of health during childhood, greater attention to nutrition and proper feeding, physical training, medical inspection of school children to detect early signs of mental or eye problems, and a vigorous antivenereal program to reduce the spread of syphilis and other venereal diseases.^{8(p32)} Believing that the nation's Public Health Service was largely a quarantine service, doctors urged its expansion for the general health and welfare of the nation, focusing attention on remedying curable defects early in life.^{3(p29)}

One physician writing for the *Journal of the Tennessee Medical Association* in Nashville suggested that among the duties of the profession in the post-war years was to study the conditions of industry and labor and adjust the science of medicine to assist in these national problems.³⁷ The medical profession, he argued, had retained too narrow a perspective of its own capacity and of its social duties. Labor, not the medical profession, had led the effort for workman's compensation and the reduction of industrial accidents and deaths. "Perhaps if our profession had been more actively, more vitally interested in bettering conditions for labor and humanizing industry," he wrote, "we would have had by this time that badly needed addition to our government, a Federal Department of Health." He went on to say:

It is imperative that we as physicians become more concerned in improving industrial conditions and in helping to restore industrial peace. With our country showing a tendency in some places of drifting towards what has already taken place in Russia and now in Germany—socialism, rioting, strikes, and bolshevism, and with the latter threatening to break out and spread like a prairie fire fanned by a strong wind, we must be on the alert and allow no opportunity to pass by without doing our bit to maintain social and industrial peace. The service that we can render is more than medical and surgical. We can help to mold public opinion, to change the attitude of the worker in the factory or mine, and to substitute personality where unfeeling cog-like interest has existed before.^{37(p437)}

Fairfax urged his colleagues in the profession to find opportunities to speak out against Bolshevism, to encourage and promote the "safety first" movement to prevent accidents, to seek early diagnosis and treatment of hook worm and tuberculosis, and to advocate a national trend in medicine toward prevention.^{37(p438)}

RETROSPECT

Overall, the Great War became an engine of change for the medical communities in Britain and the United States, serving as a catalyst for the entry of women into the profession, the recognition of certain health care personnel in military practice as well as their representation on civilian medical licensure boards, and the beginnings of a concerted effort at preventive medicine. None of these changes came easy for the professions in these countries, steeped as they were in tradition and medical orthodoxy. Nonetheless, the Great War of 1914–1918 became a leveller of sorts, whose results became more obvious in the postwar era. Perhaps medicine's greatest triumph during the war years was in the application of the science of infectious

diseases to military sanitation, with casualties from battle exceeding the mortality from communicable diseases for the first time in any major war. Similar triumphs occurred in the fight against wound infection, the remarkable use of roentgenography on a large scale, the greater understanding of gas gangrene from the bacillus *Welchii*, the importance of the mechanical principle of debridement or wound excision and the physicochemical principle of wound irrigation using the Carrel-Dakin technique, and the great impetus given to the study of shell shock and wound shock.

During the post-war years, the profession focused increasing attention on such matters as infant and maternity welfare, improved sanitation, rehabilitation of the disabled, the development of prosthetic devices, long term studies of war-gas poisoning, and the effects of the war on civilian populations. Experiments in social medicine became the focus of states attempting to bring improved medical care to rural areas and to combat venereal diseases. In the United States, this effort could be seen in the work of the Hygienic Laboratory of the US Public Health Service, the Bureau of Chemistry, and the Children's Bureau of the Department of Labor. In England, similar focus existed in the Puerperal Fever and Puerperal Pyrexia Regulations of 1926, the Ophthalmia Neonatorum Regulations, the Midwives and Maternity Act, the Adoption of Children Act, the Housing Act of 1927, and the revisions to the Maternity and Child Welfare Act of 1918. The art and science of medicine which practitioners once defined within the narrow paradigm of cure, expanded contextually during and after the war to include prevention and social medicine. The Great War brought substantive change to the world's landscape and, with it, the sphere of medical investigation and advancement took on a new meaning and direction. A corner had been turned and medicine, as an art and a science, would never again be the same.

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FROM THE LIBRARY

MASS VOLUNTEERING BY THE MEDICAL PROFESSION The Principles of Universal Service Practically Applied in a Selective Draft

In this national emergency two facts stand out pre-eminently for the consideration of the medical profession: First, that we have an army many times larger than we have had since '64; an army that is in present progress and future expectation of expansion. Second, that there must be a sufficient number of medical officers provided for that army. It is no question of choice; it is a national necessity. For, upon the efficiency of its medical department, the efficiency of the army must depend. It is not necessary to turn to historical accounts of armies beaten by disease rather than by the enemy to understand this. Anyone who is able to imagine a million men gathered together, without selection for physical fitness, upon a few square miles of ground; without sanitary supervision of their food supply or diet; without any proper selection or supervision of their water; without any sewage system and without any scientific instruction in its substitution; without carefully arranged and supervised means of waste disposal, human, animal and general; without carefully considered plans of housing and clothing; without skilled means of anticipating, recognizing, guarding against and treating the hundred potentialities of disease that always exist even among the most carefully selected group of human beings; without provision for the care and treatment of the wounded and the disposal of the dead; without detailed record of the losses by wounds or disease to justify the returned soldiers in claims for injury in their country's service, or to protect the Nation against such claims as were unjust. Can you imagine a million men under such conditions, men that are fighting for you and for every other individual in their Nation? Can you imagine their unnecessary suffering and destruction, present and future? No! You cannot imagine it; not in these enlightened days of prophylaxis. It staggers the mind. But that is what an army would be, lacking medical and sanitary provision for its selection, care and protection.

Granted, then, that the army must have medical officers. How will it get them? Why, if necessary, it will take them, whether they are willing or not. Let us be logical: We are a part of the Nation, and, although there may be a thousand other definitions of the word, a Nation in war-time is an aggregation of individuals banded together for self-defense. Now, suppose that you, as an individual, were attacked by a large enemy with a club. Would you not put up your arm to shield your head even though it might mean injury to your right hand? Why, of course, you would put up your arm in defense of your head, and just so will the Nation, when it becomes necessary, put up its medical members to protect the integrity of its combatant troops. . . .

F. T. VAN BEUREN, JR
(*NY State J Med* 1917; 17:476-478)

Myasthenic (Eaton-Lambert) syndrome in association with an indolent non-Hodgkin's lymphoma

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The myasthenic or Eaton-Lambert syndrome is a disorder of neuromuscular transmission caused by defective acetylcholine release at the presynaptic nerve terminal, which results in proximal muscle weakness that improves with repeated effort.¹ The disorder often occurs in association with intrathoracic neoplasms, especially small cell carcinoma of the lung,² as well as autoimmune disorders.³⁻⁵ The nature of these associations is unknown, but in the case of small cell lung cancer, it perhaps involves production of an antitumor antibody which cross-reacts with the neuromuscular junction.⁶ There is evidence that these IgG autoantibodies reduce the number of presynaptic calcium channels that control calcium movement into the nerve terminal.⁷ While cases of myasthenia gravis associated with high grade lymphoma have been reported,^{8,9} such an association has not been found to our knowledge in cases of myasthenic syndrome. Eaton-Lambert syndrome has been reported in acute T-cell lymphocytic leukemia in a case presenting with a mediastinal mass.¹⁰ This report describes a case of myasthenic syndrome that occurred in temporal association with a non-Hodgkin's lymphoma of low grade histology.

CASE REPORT

A 77-year-old woman had noted weakness in her lower extremities and difficulty with ambulation approximately four months prior to her final hospital admission. An electromyogram (EMG) at initial presentation had shown denervation with "high pitched sounds." Prednisone therapy, 50 mg/day, was instituted for presumed polymyositis. A biopsy of the right quadriceps femoris showed Type II fiber atrophy and a

rare focus of degenerating muscle fibers consistent with steroid treatment. Her strength improved initially during the first two weeks of steroid usage, but this improvement was transient. A subsequent EMG showed no evidence of denervation (positive waves, fibrillations) in the quadriceps. The creatine phosphokinase level was within normal limits, and screening for anti-nuclear antibody was negative. The prednisone dosage was tapered due to lack of efficacy and secondary glucose intolerance. Azathioprine therapy was begun.

The patient's medical history included aortic valve replacement for aortic stenosis, and a three-vessel coronary artery bypass graft two years prior to her present illness. Other surgeries included hysterectomy, cholecystectomy, and appendectomy. She used furosemide for chronic mild hypertension, and she had had anemia characterized by low iron and low total iron binding capacity with elevated ferritin for one year. She had no history of smoking or alcohol consumption.

Despite azathioprine therapy, the patient's weakness progressed. She sustained a weight loss of 50 pounds during one year, mild night sweats, and weakness of her voice. She was admitted to the hospital for further evaluation of her incapacitating muscle weakness. She had noticed no dysphagia or respiratory difficulties. Medications at the time of admission were methylprednisolone, 20 mg/day; azathioprine, 50 mg/day; furosemide, 40 mg/day; digoxin, 0.125 mg/day; and ferrous sulfate, 325 mg/day.

Physical examination showed a pale woman who was unable to lift her legs from the bed. Her blood pressure was 110/50 mm Hg, and the radial pulse was 80/min and regular. There was no palpable adenopathy or thyromegaly. The lung fields were clear. Prosthetic aortic valve sounds were crisp, and there was no hepatosplenomegaly. There was 3+ edema of the ankles. The cranial nerve examination was unremarkable. Ptosis was absent. Sensory examination was normal. Neck flexor and extensor strength was intact. Iliopsoas strength was 2/2, quadriceps strength 3-/3-, and ankle dorsi/plantar flexors 4/4. Deltoid strength was 4+/4+. Wrist flexor/extensor strength

handgrips, and interossei strength were graded 5-/5-. Deep tendon reflexes were diffusely and symmetrically decreased. Babinski's reflex was absent.

Admission laboratory data included the following: white blood cell count, $13,700 \times 10^9/L$ (78% segmented neutrophils, 1% band forms, 9% lymphocytes, and 11% monocytes). The hemoglobin level was 85 g/L, and the hematocrit was 26%. A platelet estimate was normal. The chemical profile showed a sodium level of 132 mEq/L; potassium, 4.7 mEq/L; calcium, 8.4 mg/dL; serum phosphate, 2.9 mg/dL; glucose, 387 mg/dL; blood urea nitrogen, 21 mg/dL; creatinine, 0.8 mg/dL; uric acid, 4.4 mg/dL; cholesterol, 125 mg/dL; albumin, 2.0 g/dL; total protein, 5.2 g/dL; bilirubin, 0.7 mg/dL; alkaline phosphatase, 277 U/L; LDH, 215 U/L; creatine kinase, 11 U/L; and aspartate aminotransferase, 24 U/mL. The serum digoxin level was 1.5 mg/dL, and the thyroid stimulating hormone level was normal at 3 mU/L. A rapid agglutination latex assay was 1:160, and a Clq binding assay was normal at 7.0%. A test for hepatitis B surface antigen was positive. A computed tomographic scan of the head showed cortical atrophy.

Electrophysiologic studies were performed with repetitive stimulation carried out via stimulating electrodes over the ulnar nerve at the wrist and recording electrodes over the belly and tendon of the abductor digiti minimi. The initial compound muscle action potential had a reduced amplitude (1.5 mV). There was a minimal decreasing response at low rates of stimulation (1 and 2 per second), and an abnormally large increment at high rates of stimulation (20 and 50 per second) to 8.5 mV (567%). A minimal increment was also noted after maximum voluntary exercise for 10 seconds. Electromyography in the biceps showed chronic polyphasic denervation changes thought to be secondary to cervical radiculopathy, and an EMG of the quadriceps femoris was normal. No myopathic signs were noted. Sensory nerve conduction velocity studies were not performed.

In view of these findings, a diagnosis of Eaton-Lambert syndrome was made, and the patient was begun on 30 mg/kg of guanidine per day. This was continued for one

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week, during which time she had deterioration in motor strength, becoming unable to lift her arms. Screening for occult malignancy was undertaken. Chest roentgenography showed no mass lesion, and a bone scan was negative. An abdominal computerized tomographic scan showed mesenteric and iliac lymphadenopathy. A biopsy of a deep left inguinal node revealed malignant lymphoma of nodular mixed type with small cleaved cells. There was suggestion of evolution to a diffuse, poorly differentiated lymphoma in a few locations. The patient was given a single cycle of chemotherapy with cyclophosphamide, vincristine, and prednisone. The lowest recorded white blood count was 2,000/mm³, and an aspiration pneumonitis developed. Cefazidime and gentamicin treatments were begun empirically. A sputum sample grew *Staphylococcus* and *Streptococcus* species. No improvement was noted in motor strength after chemotherapy, and the patient was discharged home, where she died shortly thereafter. There was no post-mortem examination.

DISCUSSION

While cases of myasthenia gravis associated with lymphoma have been reported, myasthenic (Eaton-Lambert) syndrome has not been recognized in association with lymphoproliferative disorders. A case of myasthenia gravis has been observed after treatment of a poorly differentiated lymphoma, in association with T-cell immunodeficiency, suggesting that impaired cellular immune regulation may contribute to the development of both diseases.⁹ Cases of simultaneous myasthenia gravis and T helper cell lymphoma have

also been observed, in which anti-lymphoma treatment led to resolution of the myasthenia gravis.⁸ This observation suggests that autoantibody production in myasthenia gravis may be controlled by regulatory T cells.

We report a case of the myasthenic syndrome temporally associated with a low grade, high stage non-Hodgkin's lymphoma. The neurologic findings in this case are typical of myasthenic syndrome, with proximal muscle weakness most marked in the lower extremities, sparing of extraocular and bulbar muscles, depressed deep tendon reflexes, and classic electrophysiologic findings on repetitive nerve stimulation.¹¹ The temporal occurrence of these two conditions does not prove a cause-effect relationship, but suggests an underlying deficit of T-cell immune regulation allowing emergence of abnormal B lymphoid clones manifesting as a nodular lymphoma and accompanied by production of antibodies against active sites on motor nerve terminals (presynaptic membranes).

This elderly patient with multiple disease processes and overall poor performance status did not respond to guanidine treatment or to immunosuppressive therapy. Treatment of the lymphoma was limited to one cycle of chemotherapy, so it is impossible to assess the effect of this treatment on the myasthenic syndrome. Myasthenic syndrome seen in association with other malignancies, specifically small cell lung carcinoma, has responded variably to

antitumor treatment, as reported by Clamon et al.¹²

This report serves to illustrate the need to search for malignancies of lymphoid origin as well as for small cell lung cancer and autoimmune disorders in cases of myasthenic syndrome.

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Primary pedunculated leiomyosarcoma of the lung

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Primary mesenchymal tumors account for a small percentage of all pulmonary neoplasms.¹ Primary leiomyosarcoma of the lung is a very rare tumor. Since the first reported case by Davidson¹ in 1907, fewer than 100 cases have been reported in the English literature.^{1,2} We present a case of primary pedunculated leiomyosarcoma of the lung, which to

our knowledge represents the second such reported case.³

CASE REPORT

A 65-year-old woman presented at the Methodist Hospital with dry cough and dyspnea on exertion of six weeks' duration. There was no history of smoking or exposure to asbestos. Her medical history was significant for an abdominal hysterectomy for uterine fibroids 20 years before.

Physical examination revealed dullness and decreased air entry in the right infra-axillary region. No clubbing or adenopathy was found, and the remaining examination

was within normal limits. The serum lactate dehydrogenase level was 341 U/L (normal value, 100-225 U/L). Cytologic analysis of the sputum was unremarkable. A chest roentgenogram showed a large lobular density in the right lower lung field (Fig 1). A computed tomogram (CT) showed a soft tissue mass in the right lung field near the lower portion of the right major fissure (Fig 2). Bronchoscopic findings were negative. Percutaneous needle aspiration biopsy of the mass under CT guidance revealed smooth muscle cells. However, no malignant cells were detected.

At thoracotomy, an 8 × 7 × 4-cm firm, encapsulated, well-circumscribed mass was

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FIGURE 1. Posteroanterior roentgenogram of the chest, showing a large lobular density in the right lower lung field.

found in the lower half of the right major fissure between the middle lobe anteriorly and the right lower lobe posteriorly. The mass was attached to the right lower lobe by a small pedicle. It was non-adherent to pleura and was completely excised. Microscopic examination showed spindle-shaped cells with hyperchromatic nuclei and mitotic figures, characteristic of leiomyosarcoma (Fig 3).

The patient had local recurrence six months later and received radiotherapy.

DISCUSSION

Primary leiomyosarcoma of the lung is a rare malignant tumor arising from smooth muscle.¹ Smooth muscle is present in both the bronchi and blood vessels of the lung. It is generally believed that most leiomyosarcomas arise from the bronchi. They can occur in one of the three contrasting sites within the lung: adjacent to or within a bronchus, arising from a pulmonary artery, or more peripherally in the lung parenchyma as an intrapulmonary leiomyosarcoma.^{4,5}



FIGURE 2. CT scan of the chest, demonstrating a soft tissue mass in the right lung field.

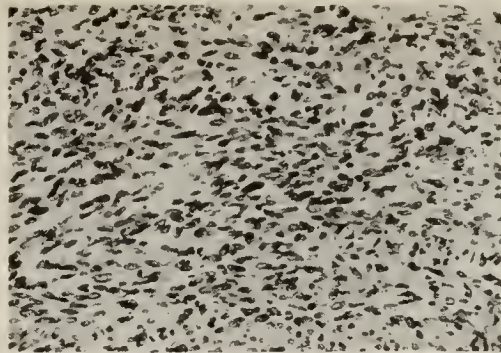


FIGURE 3. Histologic evaluation of the tumor revealed spindle-shaped cells with hyperchromatic nuclei and mitotic figures.

Leiomyosarcoma of the lung resembles bronchogenic carcinoma in its symptomatology, physical signs, and radiologic features. Almost all patients are symptomatic.² The nature of these symptoms and signs depends on the site of origin. Peribronchial and peripheral tumors usually present with cough, dyspnea, chest pain, expectoration, loss of weight, and hemoptysis.^{2,6} Occasionally, leiomyosarcoma is discovered after a routine chest radiograph. Clubbing of fingers is uncommon.^{2,7} Radiologic features in order of frequency are mass density in the lung, atelectasis, and consolidation.⁶ Associated pleural effusion and persistent pneumothorax have also been described.^{7,8}

Patients with primary leiomyosarcoma originating from the pulmonary artery usually present with dyspnea, cough, pleuritic chest pain, hemoptysis, malaise, weight loss, and congestive cardiac failure—features broadly ascribed to those resulting from right heart failure, those of distal embolization of the tumor, and systemic effects associated with the malignancy.⁵ Classically, chest radiographs show a distinctly lobulated, unilateral hilar mass projecting into the lung parenchyma in a pulmonary artery distribution.⁹ Sputum cytology is helpful in making the diagnosis, however, the diagnosis is usually made by bronchoscopy with biopsy or at thoracotomy. Although fine needle biopsy yields a diagnosis in more than 90% of malignant lung tumors, it was not helpful in this case.¹⁰ Metastasis occurs late and, when present, is mainly blood-borne. Lymph node me-

tastases are very uncommon.²

The diagnosis of primary leiomyosarcoma of the lung can only be made after exclusion of a primary tumor elsewhere (usually uterine). The patient reported here had had a hysterectomy 20 years before, and the slides on careful review were consistent with the previous diagnosis of uterine leiomyoma. A CT scan of the pelvis was within normal limits.

The prognosis is related to the degree of differentiation of the tumor and the tumor stage.^{2,11} Curative therapy has only been achieved by surgical resection. Radiotherapy and chemotherapy have been ineffective.^{11,12} Survival after excision of leiomyosarcoma of the lung is better than that of primary lung cancer, but few long term survivors have been described.²

Acknowledgment. The authors thank Dr Emil Baccash for referring this patient, and Ms Millie Casanova for her secretarial assistance.

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Severe hypokalemia and ventilator-dependent, generalized paralysis

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Skeletal muscle paralysis is a rare complication of severe hypokalemia. Concomitant hyperchloremic metabolic acidosis may be an additional risk factor for the development of skeletal muscle paralysis. We present a case of severe hypokalemia which rapidly progressed to flaccid quadriplegia requiring mechanical ventilation; the patient had underlying distal renal tubular acidosis.

CASE REPORT

A 38-year-old woman was brought to the emergency room with progressive weakness over a period of several days. The weakness initially began in her lower extremities, and on the day of presentation she was unable to walk. Fever, dysphagia, dysarthria, and visual disturbances were denied. A mild respiratory infection had occurred three weeks earlier. She had lost 30 pounds over the preceding three months due to a dieting effort consisting mostly of soft drinks and tea. She denied other significant medical history, had no recent diarrhea, and was not taking any medications.

Physical examination revealed an obese woman, comfortable, alert, and fully oriented. She was afebrile, with a blood pressure of 92/58 mm Hg; pulse rate, 56/min and regular; and respirations, 24/min. Symmetrical grade 1 to 2 muscle strength, more prominent proximally, was seen in her upper and lower extremities. The muscles appeared grossly normal and were nontender. Plantar responses were flexor, and deep tendon reflexes were normal in the upper extremities but diminished at the knees and ankles. No cranial nerve abnormalities or sensory deficits were noted.

Areflexic flaccid quadriplegia developed over the ensuing three hours with pulmonary vital capacity decreasing from 1,500 mL to 500 mL; mechanical ventilation became necessary. Blood chemistry studies from samples drawn on admission revealed a

hyperchloremic, hypokalemic metabolic acidosis, with a serum potassium level of 1.6 mmol/L; chloride, 117 mmol/L; carbon dioxide-combining power, 11 mmol/L; inorganic serum phosphorus level, 1.2 mg/dL; arterial pH, 7.21; and urinary pH, 8. Levels of magnesium, calcium, and creatinine were normal. An electrocardiogram revealed changes typical of hypokalemia.

After 30 hours of aggressive potassium replacement using both the chloride and phosphate salt, marked recovery of muscle strength occurred. At extubation, the serum potassium level was 3.7 mmol/L, while the serum phosphorus level remained low at 1.3 mg/dL. The patient's reflexes normalized and muscle strength increased to grade 4 in the upper extremities and grade 5 in the lower extremities. Residual weakness was believed secondary to possible rhabdomyolysis caused by hypokalemia and/or hypophosphatemia. Creatine phosphokinase enzymes were never elevated, but the urine was transiently positive for myoglobin. Muscle weakness resolved over the next few days, and the electrolyte levels were maintained within normal limits with daily oral supplementation of potassium, bicarbonate, and phosphorus. The patient was discharged from the hospital on these medications and continued to do well at three months' follow-up.

DISCUSSION

A diagnosis of distal renal tubular acidosis (RTA) is easily made on the basis of this patient's admitting chemistries.¹ Hypokalemia was due to a combination of renal potassium wasting and possible dietary deficiency. Hypokalemia not due to intracellular shift represents true potassium deficit. Neuromuscular symptoms associated with depletion hypokalemia are variable, but weakness is not usually seen before the serum potassium level is less than 2.5 mmol/L—paralysis can occur below 2 mmol/L.^{2,3}

Coexistent hyperchloremic acidosis may worsen the presentation of hypokalemia. Acidosis in general depresses neuromuscular membrane excitability.³ Hyperchloremic acidosis may pro-

duce up to a 1.5 mmol/L increase in potassium for every 0.1 unit decrease in pH.⁴ In contrast, respiratory and organic acidosis (lactic acidosis and ketoacidosis) produce little or no increment in serum potassium.⁵ It follows that hypokalemia with concomitant hyperchloremic acidosis represents severe depletion and may increase the likelihood of serious neuromuscular manifestations at a given level of serum potassium.

Neuromuscular manifestations of hypokalemia follow a distinctive pattern which may simulate Guillain-Barré syndrome (GBS). Initial symptoms include paresthesias and weakness in the arms and legs, followed by an ascending symmetrical flaccid paralysis which may involve the muscles of respiration.² Deep tendon reflexes may initially be intact, but they become progressively depressed with worsening muscle paralysis.² This patient was initially suspected of having GBS. Hypokalemic paralysis simulating GBS is documented in a few case reports,⁶⁻⁹ but is not mentioned among a listing of differential diagnoses included in official criteria,¹⁰ and we found it discussed in only one major text.¹¹ Of note, this is only the second case in which the initial presentation of RTA was mistaken for GBS. (The previous case involved a 47-year-old woman with distal RTA.⁸) Hypophosphatemia may also resemble GBS.¹² It is possible that in certain clinical settings other electrolyte derangements may present a similar picture.²

This case and the others cited in the literature serve to reinforce the importance of early electrolyte determination in the proper diagnosis and management of rapidly progressive weakness. Clinicians should be aware that hypokalemic paralysis may present a clinical picture initially indistinguishable from GBS. In the presence of hyperchloremic acidosis, patients who present with a serum potassium level of 2 mmol/L or

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less and a pH of 7.20 or less are at increased risk of skeletal and respiratory muscle paralysis and require aggressive treatment.^{8,13,14} Correction of hypokalemia must take precedence over attempts to buffer the pH.

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Isolated common iliac artery aneurysm

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Isolated iliac artery aneurysms occur infrequently and are quite rare when limited to the common iliac artery. These lesions are found in less than 0.5% of all aortic and iliac artery aneurysms in postmortem studies,¹ and in less than 1.5% of those reported in case reviews.^{2,3} The natural history of these aneurysms is one of progressive enlargement and often fatal rupture. There appears to be uniform agreement that for this reason early surgical treatment is essential. The original therapeutic approach to these aneurysms was one of ligation, as reported by Mott.⁴ Other approaches include wiring,⁵ resection with grafting,⁶ and resection with cross-over bypass.⁷ Here we present a rare case of a right, isolated common iliac artery aneurysm and its management.

CASE REPORT

A 67-year-old man presented to Mercy Hospital's emergency room with acute right-sided abdominal pain of 48 hours' duration. The pain was sharp and radiated to the right groin. The patient gave a history of nephrolithiasis, but stated that he had passed the calculus spontaneously. He denied any changes in bowel or bladder habits. He had no surgical or medical history of significance. Physical examination revealed a

well-developed, well-nourished man with stable vital signs and no fever. The abdomen was soft, without tenderness or any pulsatile mass. There was mild right costovertebral angle punch tenderness. Distal pulses in the lower extremities were normal. Plain abdominal films showed a questionable right ureterovesicular calculus.

The patient was admitted with a diagnosis of ureteral colic. Further evaluation by intravenous pyelogram demonstrated a double ureter on the right and a finding suggestive of a right iliac artery aneurysm. On computed tomographic (CT) scan of the abdomen, a 4-cm right fusiform, common iliac artery aneurysm was detected. An aortoiliac arteriogram (Fig 1) showed the aneurysm to be 2 cm from the aortic bifurcation and involving the bifurcation of the common iliac artery into its internal and external branches.

Following a urologic workup and finding of the aneurysm, the patient was transferred

to the surgical service. Surgery to repair the aneurysm was performed the morning following its detection. An oblique incision was made in the right lower quadrant of the abdomen, and the aneurysm was approached extraperitoneally. Upon entering the retroperitoneal space, the aneurysm was immediately apparent. Its lateral wall was grossly calcified, and the posterior surface was firmly adhered to the right iliac vein. The aneurysm extended proximally up to the bifurcation of the aorta but without aneurysmal dilation of the aorta. Distally, the aneurysm extended to the bifurcation of the common iliac artery.

One clamp was placed distally to the origin of the left common iliac artery; other distal clamps were placed on the right internal and external iliac arteries. Proximally, the aorta was clamped below the renal arteries. The aneurysm was opened longitudinally and its wall trimmed. Due to aneurysmal impingement of the aortic bifurcation, a unilateral bypass graft could not be used. The aorta was divided at its more distal aspect, followed by removal with the right common iliac artery and a 3-cm cuff of left common iliac artery. A 16 × 8-mm preclotted, knitted-dacron bifurcation graft was anastomosed to the distal aorta and the common iliac arteries bilaterally (Fig 2). The entire procedure was performed without violating the intraperitoneal cavity.

The patient tolerated the procedure without difficulty. After surgery, he had excellent distal pulses; his uncomplicated course included the start of a regular diet by the third postoperative day. He was discharged from the hospital on the sixth postoperative day. One-year follow-up shows that he has continued to do well, with no further symptoms of peripheral vascular disease.



FIGURE 1. An anterior oblique view of the aortoiliac angiogram demonstrating the 4-cm common iliac artery aneurysm.

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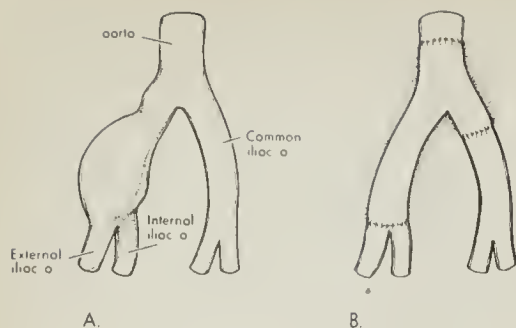


FIGURE 2. Outline representing the preoperative aneurysmal dilation of the right common iliac artery (A) and that vessel following repair with a bifurcation graft (B) (illustration by the Medical Illustration Department, State University of New York at Stony Brook, K. Gebhart).

DISCUSSION

While much has been written about aortic and aortoiliac aneurysms, the lack of reports describing isolated aneurysms of the common iliac artery underscores the rarity of these lesions. In fact, isolated aneurysms of the iliac artery are ten times less common than abdominal aortic aneurysms,⁸ despite atherosclerosis being a common cause for both.

Isolated iliac artery aneurysms are usually large at initial presentation. It is estimated that the aneurysm enlarges in size by 0.4 cm per year.⁹ The average diameter at the time of rupture has been reported to be 5.4 cm, though aneurysms of the common iliac artery tend to be larger.¹⁰ Often the patient is asymptomatic prior to rupture of the aneurysm. However, diagnostic findings may include a pulsatile abdominal, rectal, or vaginal mass. One patient has been reported to have presented with pulsatile micturition.¹² In one review, only 36% of the patients with iliac artery aneurysms had a palpable mass.² Most presenting symptoms are unrelat-

ed to the aneurysm. As in the patient reported here, many patients present with symptoms that are referable to the genitourinary system.^{3,13,14} Presenting symptoms such as urinary retention and dysuria, intestinal pain, small bowel obstruction, and back and leg pains may occur. Iliofemoral venous occlusion manifesting as leg edema may also be found as a presenting complication.¹⁵ This patient was at high risk of venous occlusion given the nature of aneurysmal impingement on the right iliac vein. Fortunately, this complication did not occur, and further immediate risk was avoided by surgical repair of the aneurysm.

A review of the literature suggests that the risk of rupture of iliac artery aneurysms is as high as 35%. Emergency surgery involving excision and replacement of the ruptured iliac artery aneurysm is associated with an extremely high mortality.⁷

Early management of an isolated common iliac artery aneurysm approaching lethal capacity is indicated. We believe that the extraperitoneal approach offered a distinct advantage in treating this patient, as there was no prolonged postoperative ileus or pulmonary complications, and his postoperative hospital stay was brief.

Most often, common iliac artery aneurysms are associated with abdominal aortic aneurysm. It has been shown that patients with abdominal aortic aneurysm often have generalized arteriomegaly,¹⁶ and in some cases diffuse biochemical changes.¹⁷ This suggests a possible systemic susceptibility to aneurysmal formation and supports the need for a closer long term follow-up of the patient with an isolated common iliac artery aneurysm.

Acknowledgment. The authors thank Harry S. Soroff, MD, Professor, Department of Surgery at State University of New York at Stony Brook, for his support, and Michelle Rider for typing this manuscript.

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Address correspondence to Editor, New York State Journal of Medicine, 420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication after editorial review. All letters are personally acknowledged by the Editor.

Systemic sclerosis possibly caused by 5-fluorouracil

TO THE EDITOR: I read the article by Marino et al¹ in the February 1990 issue of the *Journal* with great interest. A diagnosis of systemic sclerosis of this 77-year old man was inevitable in view of the clinical findings. However, I am intrigued with the patient's age at diagnosis.

In all of the 25 cases of malignancies associated with systemic sclerosis in the Pittsburgh study,² and the eight such cases in the Toronto study,³ patients' ages at diagnosis were lower than the age of the patient reported by Marino et al. I suspect that the 5-fluorouracil used for the therapy of his colon cancer, rather than the cancer itself, played a crucial role in the pathologic mechanisms of the scleroderma-like skin changes.

I believe that this case ought to be further reviewed with consideration given to the possibility that this is the first report of 5-fluorouracil induced skin changes. For a more complete case report, I would like to have further information about the RA latex test, the level of serum creatine kinase, and the chest radiography with or without existence of pulmonary fibrosis. I would also like to know the radiographic findings of the hand and fingers to clarify whether the diagnosis was systemic sclerosis with or without CREST syndrome.

Lastly, I found no reports of 5-fluorouracil associated systemic sclerosis published in Japanese.

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2. Roumm AD, Medsger TA Jr: Cancer and systemic sclerosis. An epidemiologic study. *Arthritis Rheum* 1985; 28:1336-1340.

3. Lee P, Alderdice C, Wilkinson S, et al: Malignancy in progressive systemic sclerosis—association with breast carcinoma [letter]. *J Rheumatol* 1983; 10:665-666.

In reply. We are pleased to respond to

Dr. Akama's remarks concerning our patient.¹

In the article cited by Roumm and Medsger,² seven of the 25 patients were over age 65 and four of these seven were over 70. Their oldest patient was 77, as was our patient. Lee et al³ reported on eight patients with breast carcinoma. There was a younger group of patients with a mean age of 51.8 which is in keeping with the incidence in a female population which may range from below 40 to over 80.

We did comment in our article about the possibility of a fluorouracil (5FU) induced disease process, but also commented on the past use of 5FU to treat scleroderma as reported by Casas.⁴ A rheumatoid factor test was not performed, as the patient clearly had scleroderma and the antinuclear antibody was negative. The CPK was normal as was a chest radiograph. No calcifications were noted on hand films, perhaps because the entire duration of the disease prior to expiration was only seven months.

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Ray Brook State Tuberculosis Hospital

TO THE EDITOR: It was very gratifying to read the review by Drs Wright, Monroe, and Beck of the history of Ray Brook State Hospital for Incipient Tuberculosis, as it was called in 1938 when I was a four-month summer resident along with five others.¹

It was an invaluable experience, in a beautiful atmosphere, with the

main building resembling an elegant hotel.

Although I did not expect to become a psychiatrist then as I later did, I had just read Thomas Mann's *Magic Mountain*, and found a comparative study of his characters with patients at Ray Brook fascinating.² Although Dr Bray was not around much at the time, having come down with tuberculosis himself, the teaching was excellent. I left with a feeling of confidence in diagnosing diseases of the lung which served me well in my few years in general medicine.

Something not mentioned in the review was the technique of collapsing the lung in seriously ill patients. They were required to have complete bed rest, with a sandbag on the most diseased side of the chest. This was perhaps a desperate last resort.

I am indebted to Drs Wright, Monroe, and Beck for their article and the memories it elicited.

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1. Wright KW, Monroe J, Beck F: A history of the Ray Brook State Tuberculosis Hospital. *NY State J Med* 1990; 90:406-413.

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In reply. On behalf of the coauthors and myself, I wish to respond to Dr Shainness' gracious letter concerning our article, "A history of the Ray Brook State Tuberculosis Hospital."¹ I wish to address in particular her remark about our not having mentioned the treatment of tuberculosis by collapse of the lung. This, we believe, would be a worthy subject for a separate paper.

The treatment of pulmonary tuberculosis during the past 100 years has included some drastic nonsurgical and surgical measures the purpose of which was to rest the affected portion of the lung. Collapse, mentioned by Dr Shainness, was one of these. Such measures were alluded to in an earlier paper by one of us.²

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Fatal pneumococcal infection: Another plea for the pneumococcal vaccine

TO THE EDITOR: In the past four years we have treated two middle-aged, asplenic patients who have died from overwhelming pneumococcal sepsis. Neither had received the polyvalent pneumococcal vaccine.

Patient 1 was a 56-year-old man who had had a splenectomy eight years earlier following trauma. He presented with a left lung infiltrate and hypotension. In spite of ventilator support, fluids, pressor agents, and antibiotics, he died in shock eight hours after admission. Blood cultures and lung cultures grew *Streptococcus pneumoniae*.

Patient 2 was a 49-year-old man who had had a splenectomy ten years earlier for familial hereditary spherocytosis. He presented with fulminant disseminated intravascular coagulation in association with a right lung infiltrate. In spite of ventilator support, fluids, cryoprecipitate, platelets, pressor agents, and antibiotics, he died in shock ten hours after admission. Blood and sputum cultures grew *Streptococcus pneumoniae*.

Streptococcus pneumoniae still represents the most frequent cause of community acquired pneumonia among patients requiring hospitalization.¹ Twenty to 30% of adults with pneumococcal pneumonia have bacteremia, which increases the case fatality rate to two to five times higher than that of nonbacteremia cases.¹ Present recommendations for the 23-valent polysaccharide vaccine against disease caused by *Streptococcus pneumoniae* include the asplenic patient.²

The two patients described here had no other associated illnesses increasing their risk for pneumococcal infection, other than asplenia. Accordingly, we urge clinicians to administer the pneumococcal vaccine in patients with anatomical or functional asplenia as recommended by the Centers for Disease Control.

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1. Mufson MA: Pneumococcal infections. *JAMA* 1981; 246:1942-1948.

2. Centers for Disease Control, Department of Health and Human Services, Atlanta, Georgia. Update: Pneumococcal polysaccharide vaccine usage—United States Recommendation of the Immunization Practice Advisory Committee. *Ann Intern Med* 1984; 101:348-350.

Dressler's syndrome and facial paralysis

TO THE EDITOR: In 1986, Kraus and Massey¹ reported on three patients with idiopathic facial paralysis (Bell's palsy) in temporal association with acute myocardial infarction; the authors hypothesized that the probability of these events occurring together by chance alone is small. Carratalá et al² doubted this association, because two of these patients were hypertensive, and the relationship of this factor and facial palsy is known.³ One of the patients also had diabetes, and in the third case, the facial palsy appeared three weeks after the myocardial infarction. We report on a patient with acute myocardial infarction in whom both postmyocardial infarction syndrome, or Dressler's syndrome, and acute facial paralysis developed.

Case Report. A 95-year-old woman presented with a five-day history of left-sided facial weakness. This was preceded by two weeks of nonspecific symptoms including anorexia, fatigue, and a nonproductive cough. Her blood pressure on admission was 140/80 mmHg, and an electrocardiogram (ECG) showed a recent inferior wall myocardial infarction when compared to an ECG obtained several weeks prior to admission. Serial cardiac enzyme tests were negative. Chest radiographs showed bilateral pleural effusions and a prominent heart.

The patient subsequently experienced pleuritic chest pain, a pleuropericardial rub, fever to 101°F, anemia, and an elevated white blood cell count and erythrocyte sedimentation rate. Computed tomography showed pleural and pericardial effusions, and echocardiography showed hypokinesis of the inferior cardiac wall. The antinuclear antibody titer was 160 (normal range, 0-20) with homogeneous and speckled patterns. The hospital course was complicated by episodes of atrial flutter. The facial paralysis resolved in the ensuing three weeks.

Discussion. Postmyocardial infarction syndrome, first described by Dressler,⁴ has an incidence of 1% or less following an acute myocardial infarction. Between two and ten weeks after the infarction, symptoms of pericarditis, pleuritis, fever, and malaise occur. There may be pleural and pericardial effusions, leukocytosis, anemia, an elevated sedimentation rate, and ST-segment elevations on the ECG. The syndrome usually resolves without complications, but symptoms may recur.

The facial paralysis observed in this patient was almost certainly due to a peripheral defect in the facial nerve and not to a central lesion, as the left forehead was not spared. There was no evidence of trauma, Lyme disease, diabetes, sarcoid, tumor, or herpes zoster oticus, conditions that have been associated with facial paralysis.

This is the first report of a temporal association between facial paralysis and Dressler's syndrome, and the fourth report of an association between facial paralysis and acute myocardial infarction. Whether these associations represent cause and effect or whether there is an underlying pathogenesis is unclear. The etiology of Dressler's syndrome is unknown, although Dressler believed—and subsequent evidence has supported—that it is an autoimmune reaction to released myocardial antigens. Similarly, while no conclusive cause of Bell's palsy has been identified, one theory implicates herpes simplex virus reactivation with subsequent immunologic damage to the facial nerve as a possible cause.⁵

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BOOK REVIEWS

THE NUCLEUS OF CARDIAC DIAGNOSIS: ELECTROCARDIOGRAPHY AND CHEST X-RAY

By William A. Schiavone, DO. 287 pp, illustrated. Philadelphia, Lea & Febiger, 1990. \$34.00 (softcover)

This is a time of endless publications about cardiological subjects, and one wonders if yet another can serve any purpose. True, technical advances in the subject have been so extensive and have appeared so rapidly that a large expansion in cardiac literature is understandable and fairly reasonable, but one gets to the point of saying enough is enough.

Yet, here is a new softcover book with a slightly different twist. It emphasizes the significance and usefulness of the routine electrocardiogram and chest film, particularly the chest film, in the diagnosis of heart disease.

These days red flags are raised at the cost of new technology (echocardiograms, angiograms, CAT scans, and NMRs) and their indiscriminate use. Although the author does not emphasize the significance of the simplest and still least costly examinations, the history and physical examination, he does use a series of 75 case reports to indicate the importance of the next least costly tests, the electrocardiogram and the chest film. In fact, in his preface he likens these two tests to the nucleus of a living cell, with the "protean" history as the cell protoplasm and the physical examination as the cell membrane. He emphasizes the chest film because, he states, "so little is written about its use in the diagnosis of cardiac disease."

These 75 cases, all originating from the Cleveland Clinic during the author's time there as staff cardiologist, illustrate most of the types of heart disease encountered by the cardiologist, such as coronary disease, myocardial disease, valvular disease, pericardial disease, aortic disease, congenital disease, pulmonary disease, pacemaker problems, skeletal deformities associated with heart disease, and conditions mimicking heart disease.

The cases are concisely and provocatively presented to challenge the student of cardiology, as well as to illustrate how definitive diagnoses can actually be made, or at least indicated, by the electrocardiogram and the chest film. They are presented in such a way

as to give the readers one clue after another to stimulate their diagnostic acumen. With many little pearls in the text, this type of presentation makes it suitable as a review for aspiring residents and fellows in cardiology, not as a complete review by any means, but as an indicator for the need of more in-depth reference review.

The information in the case material is accurate, but somewhat sketchy, perhaps intentionally so. The illustrations of chest films are large enough and clear enough to serve their purpose, but the electrocardiograms, although satisfactory examples, could have been larger and time lines could have been included. Had the pages been somewhat larger and the electrocardiograms larger, the volume's purpose might have been better served, in spite of the added expense. There is an index for ready reference, but no bibliography.

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PEARLS AND PITFALLS IN ELECTROCARDIOGRAPHY

By Henry J. L. Marriott, MD. 158 pp, illustrated. Philadelphia, Lea & Febiger, 1990. \$17.50 (paperback)

This is an excellent monograph on the practical points of surface electrocardiography. The author, a world-renowned expert in electrocardiogram (EKG) interpretation, intended this book to be of practical use in making the correct EKG diagnosis, and did not intend it to be a basic and comprehensive text book of EKG interpretation. The book contains over 150 pages of sample 12-lead EKGs and rhythm strips, accompanied by their interpretations. It is organized into four parts: "Mostly Arrhythmias," "Unheavenly Twins" (which contains differential diagnostic points of various EKG phenomena), "Mostly Blocks," and "12-Lead Revelation" (which contains useful points in 12-lead EKG interpretations). Since this book contains examples illustrating somewhat unrelated points, organization is arbitrary and indexing for quick reference is difficult. The author's style of presentation makes this monograph both entertaining and easy to read. This is one of the few books on surface EKGs written in

this style. An additional virtue of this book is the frequent reference to the literature on modern cardiac electrophysiology. I strongly recommend this book for more serious students of electrocardiography including medical residents and cardiology fellows.

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FLEXIBLE SIGMOIDOSCOPY: TECHNIQUES AND UTILIZATION

Edited by Melvin Schapiro, ME, and Glen A. Lehman, MD. 227 pp, illustrated. Baltimore, Md, Williams & Wilkins, 1990. \$45.00 (hardcover)

Among all of the books on the basics of lower gastrointestinal (GI) endoscopy published during the 1980s, this represents one of the best efforts to date. Both authors were involved with the pioneering conjoint agreement between the American Academy of Family Physicians and the American Society of Gastrointestinal Endoscopy, which created a looseleaf textbook somewhat similar to this one. The authors have expanded upon the original AAFP-ASGE effort.

It is gratifying to see these gastroenterologists moving away from the previous fixation on 35 cm flexible sigmoidoscopy, and acknowledging the usefulness of the longer 60-70 cm instruments. Many of these techniques and comments are applicable to those primary care physicians who are now advancing to the use of full length colonoscopy. These authors, however, are careful to maintain the specialty position which generally discourages the performance of full length colonoscopy by primary care physicians. Nevertheless, Medicare has now created a relative financial disincentive for flexible sigmoidoscopy as compared to colonoscopy.

The chapter on the fiscal implications of GI endoscopy is excellent. For the practicing physician, certain additional information would be very helpful. For example, Medicare, in response to increasing volumes of charges, dramatically reduced fees for flexible sigmoidoscopy during the 1980s. Colonoscopy fees have been reduced less dramatically, but these fees still repre-

sent a financial bonanza for most primary care physicians. Since patient care is enhanced simultaneously, these economic forces and scientific benefits will drive more and more primary care physicians into the use of full length colonoscopy and polypectomy. Training standards for these GI endoscopy procedures are suggested, but the training recommendations for hospital-based privileges remain more political than scientific. This challenge will return with a vengeance as capitated government health plans evolve later in the decade.

This book contains several important chapters not found in many similar textbooks. The sections on organizing the office and bowel preparation are very well done. Some mention might have been made of the work of Paul Williams, MD, and Marilee Williams, RN, who wrote a similar chapter for the AAFP-ASGE textbook. The book generally gives little credit and mentions no literature from the family practice groups that courageously pioneered this technique in the early 1980s.

The book is well written and produced. It is a good value compared to its most similar competitor (the AAFP-ASGE looseleaf textbook). It should be required reading for primary care physicians who wish to enhance their lower GI endoscopy skills.

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ANNUAL PROGRESS IN CHILD PSYCHIATRY AND CHILD DEVELOPMENT 1989: A SELECTION OF THE YEAR'S OUTSTANDING CONTRIBUTIONS TO THE UNDERSTANDING AND TREATMENT OF THE NORMAL AND DISTURBED CHILD

By Stella Chess, MD, and Margaret E. Hertzog, MD. 576 pp, illustrated. New York, Brunner/Mazel Publishers, 1990. \$50.00 (hardcover)

Since the body of knowledge in child psychiatry and child development is rapidly expanding, the task of monitoring and selecting appropriate material from the numerous research studies and publications of the United States and other countries is enormous. The editors of this volume have been successful at the task of compiling this annual update.

Stella Chess, MD, is Professor of Child Psychiatry at New York University Medical Center and author of the well-known and widely used textbook *Principles and Practice of Child Psychiatry*. Her contributions to research in child development are outstanding. She, together with Alexander Thomas, MD, initiated the now famous New York Longitudinal Study over 25 years ago, which established the importance of individual temperament in the developmental process in normal circumstances and behavior disorders. The results of this study were presented in previous publications. Dr Chess also wrote *The Dynamics of Psychological Development and Origins and Evaluation of Behavior Disorders*. She received the 1980 Blanche F. Ittleson Prize for *Research in Child Psychiatry*.

Margaret E. Hertzog, MD, is Associate Professor of Psychiatry at the Cornell University Medical College, Director of the Child and Adolescent Outpatient Department, and Medical Director of the Nursery School Treatment Center, Payne Whitney Clinic at New York Hospital. She is also the author of numerous research and clinical papers. Alexander Thomas, MD, resigned as the co-editor after many years of outstanding contributions to the publication.

The 1989 volume of this annual series is a continuation of outstanding service. It covers a broad selection of topics that are of vital interest to child care professionals working with normal and disturbed children and adolescents. The book consists of 33 articles, distributed among nine major areas of interest: infancy studies, developmental studies, gender and race, special stress and coping, temperamental studies, depression and suicide, other clinical issues, adolescent issues, and special issues.

All of the articles, whether original or reviews, provide stimulating material of great interest to child care professionals. It is difficult to single out any one without neglecting another. In the area of infancy studies, the article, "Infant Imitation and Memory: Nine-Month-Olds in Immediate and Deferred Tests," highlights the ability of nine-month-old infants to imitate simple actions immediately and after a delay period.

In the area of developmental studies, "The Nature-Nuture Debate; Aptitudes and Group Differences," reviews and challenges the notion of immutability of intelligence and aptitude. In the same section another article titled "In-

fant-Adult Attachment on the Kibbutz and Their Relation to Socio-emotional Development Four Years Later," highlights the significance of the quality of the infant's secure attachment to a caregiver. "The Adult Outcome of Early Behavioral Abnormalities," provides a selective review of adult outcomes of some of the childhood disorders.

In the area of gender and race, "Race and Gender as Psychological Variables: Social and Ethical Issues," reviews social and ethical issues related to research dealing with race and gender.

In the next section on special stress and coping, "Children Who Witness the Sexual Assaults of their Mothers" examines the traumatic responses of ten children who witnessed the sexual assault of their mothers. The authors suggest that the children be given special diagnostic attention and therapeutic intervention. Another clinical study in the same section, "Single-Parent Families: Child Psychiatric Disorder and School Performance," examines the association between single-parent family status and child psychiatric disorder as well as poor school performance. The authors indicate that poverty and family dysfunction are the most significant variables related to outcome. "Issues of Adolescent Development for Survivors of Childhood Cancer" highlights those findings indicative of the ability of adolescents to make a fairly good adjustment in the majority of cases. In the area of temperamental studies, "Moving Away from the World: Life Course Patterns of Shy Children," suggests that shyness persists across the life course.

The section on depression and suicide has five articles providing an excellent update in an area of great significance to mental health professionals dealing with children and adolescents. "Normal Children at Risk for Suicidal Behavior: A Two-Year Follow-up Study," provides data on the prevalence of suicidal ideas among normal preadolescent children, estimated to be between 8.9% and 17.9%. Another paper in this section, "Completed Suicides in Children and Adolescents," examines the records of 229 youths in two Minnesota counties who died of suicide over a ten-year period.

The section on other clinical issues has an article titled "Children's Knowledge and Attitudes About AIDS." The findings of this study suggest that factual information regarding AIDS does not influence attitudes and hypothetical behavior in children.

In the section on adolescent issues the chapter "Neuropsychiatric Psychoeducational and Family Characteristics of Fourteen Juveniles Condemned to Death in the United States" presents the data from a study of 14 such adolescents.

The final section addressing special issues has a review article by Dr Stella Chess, "Child and Adolescent Psychiatry Come of Age: A Fifty-Year Perspective." It provides readers with a survey of the major developments in child and adolescent psychiatry over the past 50 years. The other article in this section, "Day Care and Its Effects on Children: An Overview for Pediatric Health Professionals," is helpful for all those who are in the position of helping the parents of young children to evaluate arrangements for child care.

Each of the nine sections is preceded by the editors' review, written in a clear cohesive style, highlighting the most relevant issues in the articles. The book is well organized and typographically clear. The hard cover is a cheerful orange with title in black, providing a nice contrast.

This 22nd edition of *Annual Progress in Child Psychiatry and Child Development* fulfills the promise of its subtitle: "A Selection of the Year's Outstanding Contributions to the Understanding and Treatment of the Normal and Disturbed Child."

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WITHIN OUR REACH: BREAKING THE CYCLE OF DISADVANTAGE

By Lisbeth B. Schorr with Daniel Schorr. 432 pp. New York, Anchor Press, 1988. \$19.95 (hardcover)

We are more knowledgeable and prepared to tackle the problems of children and families living in the "cycle of disadvantage" than we would care to admit. Lisbeth and Daniel Schorr leave no social, political, economic, or ethical issue uncovered in their presentation of the realities and possibilities of changing life outcomes for the next generation of disenfranchised youth.

The dimensions of disadvantage are many and pervasive: poverty, lack of resources, limited education, social isolation, lack of opportunity, and lack of access to mainstream society. The authors point out that in past generations, ghettos

to dwellers who could work, save, and leave the community did so. Today, the inner city ghettos no longer have that critical mass of stable, achievement-oriented families to provide neighborhood cohesion, support, pride, and sanctions. The remaining families have the odds stacked against them because of the intense concentration of problems and dismal prospects for the future. The problems of the inner city ghettos are not the fault or responsibility of their children. Neither should it be their legacy.

Within Our Reach contains several excellent examples of prevention/early intervention programs that have succeeded in helping at risk children and families. The model programs include efforts at improving prenatal care; reducing early and unplanned teen pregnancies; providing child health services, school based health services and family support services; and providing early child care and education. The programs were conducted in several urban poor communities in various locations throughout the United States. The programs utilized combinations of economic supports including federal and state funds. All of the programs found their successes related to their community focus, comprehensive network of services, creative approaches to problem solving, accessibility, continuity, quality of services, and commitment of their workers to the community. All of the programs were successful in preventing or changing negative outcomes for individuals, families, and groups.

The authors clearly explain the issues and problems that face those that seriously want to reach out and break the cycle of disadvantage. We have inherited a history of years of disadvantage that is getting worse. We face powerful political, professional, and administrative forces that are neither flexible nor easily changed. We face financial accountability, yet the cost effectiveness of prevention/early intervention programs is difficult to measure. We lack the attractiveness, prestige, and financial rewards to recruit and retain dedicated professionals. Our current political climate supports budget trimming, therefore budget appropriations do not keep pace with needs.

This book can be highly recommended to a wide audience. Those professionals who practice in poor inner city communities know the inherent problems and frustrations of their work all too well. This book provides words of encouragement and shares what has

worked for others in similar situations. It also gives readers the incentive to prove the effectiveness of their own programs and to become more politically active for the sake of their clients. It would be an excellent resource or required text for professionals and students in the fields of public health, business, law, government, education, social work, medicine, and nursing. The book speaks of social responsibility, societal ethics, legislative policy and planning of community based programs. We all need to be reminded of what exists, of what can be, and of the power of our personal and professional beliefs and efforts.

Within Our Reach documents that we have the necessary knowledge, research, and demonstration projects and economic incentives to break the cycle of disadvantage. What we need is to increase the awareness and unity of every person in working toward a common goal: our nation's well-being and productivity. The authors suggest that a focus such as this can unite various interest groups to confront the dimensions of disadvantage and save our most precious resources, our children. Government leadership in the form of economic support, legislative policy, and political will must shine like a beacon to guide the national effort. Just as the moon and stars reflect the light of the sun, those "thousand points of light" so often mentioned by this administration need a powerful central source, too. Are the gains of saving our children a reasonable return for the cost? You decide if you think we can continue to write off entire segments of our nation forever and not suffer.

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EMBRYOS, ETHICS, AND WOMEN'S RIGHTS: EXPLORING THE NEW REPRODUCTIVE TECHNOLOGIES

By Elaine Hoffman Baruch, Amadeo F. D'Adamo, Jr, and Joni Seager. 259 pp, illustrated. Binghamton, New York, The Haworth Press, Inc, 1988. \$34.95 (hardcover)

This volume is a collection of short papers by medical professionals, historians, sociologists, ethicists, feminists, and journalists. It introduces the reader to some of the medical options, technological possibilities, and ethical issues

of reproductive technologies with an emphasis on in vitro fertilization (IVF) and prenatal screening. The book is intended as a resource and aims to "make sure that women and their lives remain visible throughout the discussion of these issues" (Editors' Preface). It succeeds in achieving this goal, including unusual perspectives such as those of the child who might have three distinct mothers (genetic, gestational, nurturing); two distinct fathers (genetic, nurturing); and the genetically defective person who, in light of our current screening technologies, might have been aborted.

The justification for the emphasis on women's perspectives is that management of most reproductive technology requires action by the woman. While contraception and abortion are necessary for the liberation of women, one persistently recurrent, haunting question is whether much of the current reproductive technologies (IVF, surrogate gestation, prenatal screening, embryo transfers, genetic manipulation of embryos, and the like), liberates or oppresses women. For example, perhaps the most shocking statement of the book is that women primarily bear the physiological burden of technologically circumventing male, as well as female, infertility:

A study of voluntarily childless couples found that it was the wishes of the husband that prevailed When the wife wanted a child and the husband did not, they stayed childless; when the husband wanted a child and the wife did not, they often divorced. In interviews with women who terminated a pregnancy following a prenatal diagnosis of genetic or developmental defect, Rothman found it was the husbands who were sure about the decision to end the pregnancy, and who persuaded their wives of the wisdom of the decision

Juxtaposed to William Ruddick's simple but decisive argument for the woman's sole right of decision is the fact that the range of choice may be enhanced more for men than for women, and decisions are often made by or through pressure exerted by men. The right is not meaningful unless it is also a right to not use the technologies. Several authors emphasize the need for practitioners and patients to remain cognizant of the imprecise nature of medicine as a science, an important consideration in light of the low success rates of IVF.

The papers collected in *Embryos, Ethics and Women's Rights* grew out of two conferences, "Embryos, Ethics, and Eugenics: A Brave New World?"

(New York, 1985) and "Women and Reproductive Technologies" (Boston, 1986). There are no subject headings in the table of contents, but Henifin's introduction is quite useful for orienting the reader to the volume's essays. For the novice, D'Adamo and McShane provide descriptive overviews of reproductive technology. Other articles discuss the discrepancy between the medical perspective and the woman patient's experience; feminist critiques; the impact of the technologies on the children; as well as social, ethical, religious and political analyses. There is some redundancy in the essays, but generally each makes a distinctive contribution. I can recommend, in particular, those by Sarah, Rothman, Lorber, Lifton, Charo, Saxton, Hubbard, and Shannon. (Lawler, the other representative Catholic, simply presents the traditional position). A partially and somewhat scantily annotated bibliography of further resources is by now somewhat dated, the latest entry being from 1986. Neither the contributors nor the editors offer solutions or answers to the complex ethical, social, and interpersonal problems and questions raised by the reproductive technologies. That is not their intent. Rather it is to sensitize us, the medical profession, patients, the public, to these questions and to remind us that medical choices are never purely "medical" decisions. In light of the ethical ramifications of these technologies, their work suggests a new and broadened meaning to the notion of "informed consent."

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SEXUAL TRAUMA IN CHILDREN AND ADOLESCENTS: DYNAMICS AND TREATMENT

By Diana Sullivan Everstine, PhD, and Louis Everstine, PhD. 206 pp, illustrated. New York, Brunner/Mazel Publishers, 1989. \$25.00 (hardcover)

The theme of this very comprehensive, well written, and well referenced book is that sexual trauma in children and adolescents has myriad presentations, far reaching consequences for both the victim and family unit, and is treatable. The purpose of this book is to help health professionals, specifically but not exclusively, therapists, to gain the cognitive tools to recognize and

treat the sexual abuse victim.

The authors' qualifications are excellent. Dr Diana Sullivan Everstine and Dr Louis Everstine each hold positions as Directors of the Emergency Treatment Center, are research fellows at the Mental Research Institute, and are President and Vice President, respectively, of Affiliated Psychologists and Counselors, Inc, Palo Alto, California. The authors' authority is evident from the book's style and in-depth contents.

This book definitely has a niche in the already bountiful literature on childhood and adolescent sexual abuse. The authors achieve this distinction by maintaining a focus on the dynamic presentations and treatment aspects from the perspective of the therapist. The book does not try to cover comprehensively all aspects of sexual abuse management. I see this as one of its strengths. To have done so, the authors would have had to either superficially cover all other areas or enlist an array of social work, nursing, and medical experts to produce an encyclopedic, long, and less readable text.

An outline of the contents can be found in the book's preface. The first chapter presents an overview of molestation. In particular, several popular misconceptions are presented. Chapter 2 offers a systematic approach for the therapist to assess whether or not a child has been molested and, if so, the extent of trauma produced. Chapters 3 and 4 outline therapeutic plans for the child and adolescent victim respectively. The next several chapters review the topics of incest, molestation of boys, and the management of the adult client who divulges a history of personal sexual victimization during childhood or adolescence. The final chapter discusses the ethical and legal considerations important to the therapist in dealing with societal issues and the courts.

The quality and accuracy of the book's contents are excellent. In addition, the book's organization and style are conducive to use by non-therapist practitioners. The clarity is also excellent. At no point does the reader feel lost in a sea of unfamiliar technical jargon. A particularly helpful feature is the recurrent use of short case vignettes as a vehicle to present information and highlight points. These brief presentations are written broadly enough to elicit patterns of recognition for the non-therapist reader who may be involved in the detection and management of sexual abuse.

In summary, the authors achieve the

book's stated objectives. I am not aware of any publication which does this as well. This is an extremely useful publication for any practitioner with a more than superficial interest in sexual abuse.

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CONTROL OF ONSET OF PUBERTY

Edited by Melvin M. Grumbach, MD, Pierre C. Sizonenko, MD, and Michel L. Aubert, MD. 710 pp, illustrated. Baltimore, Md, Williams & Wilkins, 1990. \$125.00 hardcover)

Dr Melvin Grumbach, the senior editor, is a pediatric endocrinologist who is well known for his studies of puberty. This text is a comprehensive review of the current understanding of the biology of puberty in mammals, as well as a comparison among species, specifically rats, guinea pigs, lambs, primates, and humans. In addition, clinically relevant problems of puberty are reviewed with regard to etiology, diagnosis, and treatment.

The text is divided into chapters based on oral presentations made by prominent researchers at symposia held between 1982 and 1984. Following each chapter is a question and answer section based on discussions held at the symposia. Addenda, discussions, and pertinent updated bibliographies are provided for those topics where significant advances in knowledge have occurred since the symposia were held. Each chapter includes a review of various pertinent studies as well as data which are frequently presented in graphic or tabular form. The topics follow a logical progression from fetal development through the process of puberty for both males and females, with comparison among species of testicular, follicular, and hypothalamic and pituitary development. More controversial areas regarding the behavioral aspects of puberty and melatonin are also discussed. The clinical chapters provide summaries of the experiences of contributors with regard to delayed puber-

ty and precocious puberty, as well as puberty in congenital adrenal hyperplasia, chiefly 21-hydroxylase deficiency.

This is one of the few texts dealing solely with puberty and its control. Researchers in the field of puberty will find it useful, as will interested pediatric endocrinologists.

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RYAN: A MOTHER'S STORY OF HER HYPERACTIVE/TOURETTE SYNDROME CHILD

By Susan Hughes. 153 pp. Duarte, Calif, Hope Press, 1990. \$9.95 (paperback)

Attention-deficit hyperactivity disorder (ADHD) constitutes a significant portion of the childhood psychiatric disorders which present to physicians and mental health professionals. Approximately 5% of the school-age population shows symptoms of inattention, restlessness, and impulsivity. Studies of families suggest a significant genetic role in the pathogenesis of the disorder. Accumulating evidence suggests that Tourette syndrome (TS), a common genetic neurologic condition characterized by childhood onset of involuntary motor and vocal tics, contributes significantly to the etiologic heterogeneity of ADHD. More than 50% of children with TS and tics have ADHD and significant numbers of children with ADHD have undiagnosed tics, later develop tics, or have a family history of TS.

This book is a timely contribution to the field of TS and ADHD. It appears at a time of increasing public and medical awareness of the tic disorder and its significant relationship to behavior problems of childhood. Despite this increasing awareness, misdiagnosis is frequent and parents are often blamed for their child's misbehavior.

Ryan is the story of one boy's evolving TS disorder and a mother's attempts to understand its baffling array of symptoms. It is the story of a moth-

er's devotion and love for her child despite the never ending series of temper outbursts, disruptive and defiant behaviors, and disappointments, and of her determined advocacy on his behalf. It begins with Susan Hughes' early suspicions of problems during her pregnancy and progresses through the terrible twos, a stage Ryan reaches prematurely by the end of his first year. The ensuing early school years result in new and equally difficult problems, dashing the Hughes' hopes that Ryan's problems will soon go away. The story culminates in a new beginning for Ryan and family when the Hughes receive a correct diagnosis of TS and an explanation of its relationship to the behavioral problems they have tried desperately to manage and comprehend. In the final chapters the author provides helpful advice on matters of coping strategies for parents and ways to assist the ADHD and TS child.

Susan Hughes' message to parents, physicians, mental health professionals, and educators is that the often devastating behavioral and academic manifestations of TS and ADHD are a result of neurologic dysfunction and that early diagnosis and prescriptions of appropriate medical, psychosocial, and educational interventions can greatly alleviate the burden to child and parent of these treatable disorders. She also acknowledges that some parents must struggle before they are able to accept that neurologic dysfunction may be at the root of their child's problems and that there are frequently no easy answers or solutions.

Reading *Ryan* is highly recommended to parents and family members of TS and ADHD children and to educators and health professionals. All will come away more compassionate, understanding, and effective in helping children with behavioral and learning problems.

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Urea resistant neutrophil alkaline phosphatase and screening for Down's syndrome

At present, the most effective screening tests for Down's syndrome are based on measurements of alpha fetoprotein, unconjugated estriol, and human chorionic gonadotrophin concentrations in the mother's blood. When combined with the use of maternal age as a screening factor, these methods can identify 61% of affected pregnancies, with a 5% false positive rate. In a recent study, measurements of urea resistant neutrophil alkaline phosphatase (AP) activity yielded a detection rate of 79%, without exceeding a false positive rate of 5% (*Br Med J* 1990; 301:1024-1025). The addition of this test to the current screening regimen could improve the detection of Down's syndrome.

The authors obtained blood samples from 72 women who were known to be carrying fetuses with Down's syndrome, and compared the measurements of urea resistant neutrophil AP in maternal blood to those from 156 control subjects whose fetuses did not have Down's syndrome. The blood samples were collected at 19 and 21 weeks of pregnancy for index and control patients, respectively.

Before a test for urea resistant neutrophil AP would be ready for routine use, further studies are needed to refine the levels that distinguish fetuses that have and do not have Down's syndrome, and to determine relevant levels at 16 weeks of pregnancy, when most screening is performed.

Isoniazid and acetaminophen interact to produce hepatic and renal toxicity

A 19-year-old woman on isoniazid therapy (300 mg/day) exhibited hepatic and renal toxicity after ingesting an overdose of acetaminophen, a maximum of 11.5 g—a level that would not ordinarily induce severe toxicity (*Ann Intern Med* 1990; 113:799-800). "The admission blood chemistries were remarkable only for moderate elevations in the serum transaminases and serum bilirubin." She became oliguric on hospital day three and required hemodialysis for fluid accumulation. The patient recovered following subsequent dialysis treatments.

Based on the findings from studies on persons with alcoholism, who are at increased risk for acetaminophen toxicity, the authors propose that isoniazid induces an oxidase enzyme in the liver (P450IIE1), which converts a greater than usual proportion of the acetaminophen into toxic metabolites. P450IIE1 is also present in the kidney.

Hyperactivity linked to glucose metabolism in the brain

Hyperactivity, characterized by symptoms of "motor restlessness, attentional difficulties, distractibility, and impulsiveness," is not only a childhood disorder, but persists into adulthood for 40-60% of affected children (*N Engl J Med* 1990; 323:1361-1366). The cause of hyper-

activity is not known, and no consistent neurobiologic or chemical abnormalities have been identified. Altered cerebral glucose metabolism has been proposed as a causative factor.

Zametkin et al used positron emission tomography (PET) with [18F]fluoro-2-deoxy-D-glucose to measure regional glucose metabolism in the brains of 50 adult control subjects and 25 adults who experience excessive restlessness and inattentiveness, have a history of childhood hyperactivity, and are the biologic parents of a child previously diagnosed as having an attention deficit disorder with hyperactivity.

The authors found depressed overall cerebral glucose metabolism in hyperactive patients—8.1% less than in controls. In 30 of the 60 specific brain regions evaluated, glucose metabolism was significantly reduced in hyperactive patients. The premotor and superior prefrontal regions demonstrated the greatest reduction in metabolism.

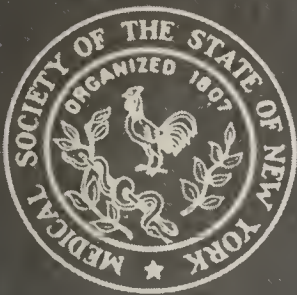
The importance of this finding is strengthened by the fact that neuropsychological tests of hyperactive children implicate the frontal lobe region. Furthermore, "Disorders of the prefrontal regions often result in inattentiveness, distractibility, and an inability to inhibit inappropriate responses."

Immunoglobulin therapy shows promise in chronic fatigue syndrome

Chronic fatigue syndrome (CFS) describes a condition of excessive tiredness that is made worse by even minimal physical exertion. The psychological component of CFS includes disruption of concentration and short-term memory; depression is a common element of the disorder. Theories to explain the immunologic disturbances evident in CFS include uncontrolled antigen stimulation from a previous viral infection which leads to excessive cytokine production.

Lloyd et al performed a double-blind study in which 49 patients with CFS were randomly assigned to receive 2 g/kg of immunoglobulin by continuous infusion once a month for three months, or a placebo (*Am J Med* 1990; 89:561-567). Patient evaluation at entry to the study and three months after the final infusion was based on physician and psychiatrist assessments of the symptoms, patient interviews, and measurements of cell-mediated immunity, including T-cell subset analysis, delayed type hypersensitivity skin testing, and T-cell stimulation.

On completion of the study, 43% of the IgG recipients and 11% of the placebo recipients were rated by the physician as exhibiting a marked reduction in symptoms. These patients all had significant improvement in measurements of cell-mediated immunity. The psychiatrist rated 38% of IgG recipients and 12% of placebo recipients as significantly improved. At six and 12 months after completion of the trial, the majority of patients who demonstrated improvement reported the return of symptoms.



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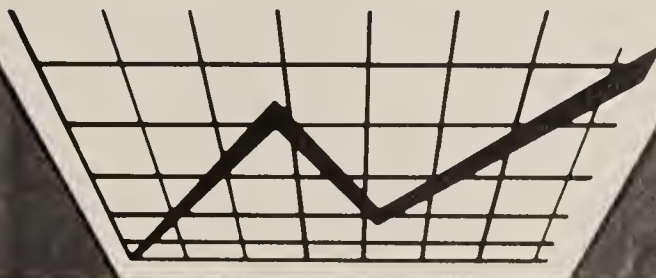
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SURVEY



YOCON[®]

YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

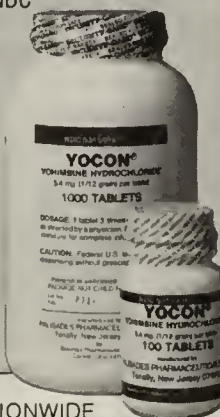
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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therapy for active
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Zantac[®] 300
ranitidine HCl/Glaxo 300 mg tablets



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DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

*See adjacent page for Brief Summary
of Product Information.*

In active duodenal ulcers

Once-a-night hs therapy controls acid rain

*Zantac 300
#30
Sig: 1 tab h.s.*

Zantac[®] 300
ranitidine HCl/Glaxo 300 mg tablets

Zantac[®] 150 Tablets
(ranitidine hydrochloride)

Zantac[®] 300 Tablets
(ranitidine hydrochloride)

Zantac[®] Syrup
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac[®] product labeling.

INDICATIONS AND USAGE: Zantac[®] is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac[®] is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac[®] therapy does not preclude the presence of gastric malignancy.

2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix[®] may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac[®]. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H₂-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

BRIEF SUMMARY

Zantac[®] 150 and 300 (ranitidine hydrochloride) Tablets
Zantac[®] (ranitidine hydrochloride) Syrup

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac[®] product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac[®] 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac[®] 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac[®] 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac[®] Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990



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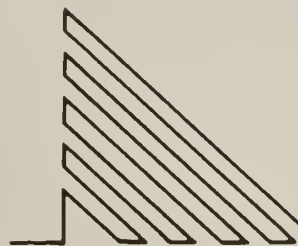
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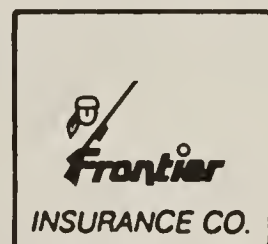
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Brief Summary.

Consult the package literature for prescribing information.
Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β -hemolytic streptococci).

Contraindication: Known allergy to cephalosporins.

Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of non-susceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:

- Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, serum-sickness-like reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055% to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
- Stevens-Johnson syndrome, toxic epidermal necrolysis,

and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.

- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypotonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

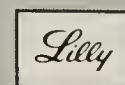
Abnormalities in laboratory results of uncertain etiology

- Slight elevations in hepatic enzymes.
- Transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia.
- Rare reports of increased prothrombin time with or without clinical bleeding in patients receiving Ceclor and Coumadin concomitantly.
- Abnormal urinalysis; elevations in BUN or serum creatinine.
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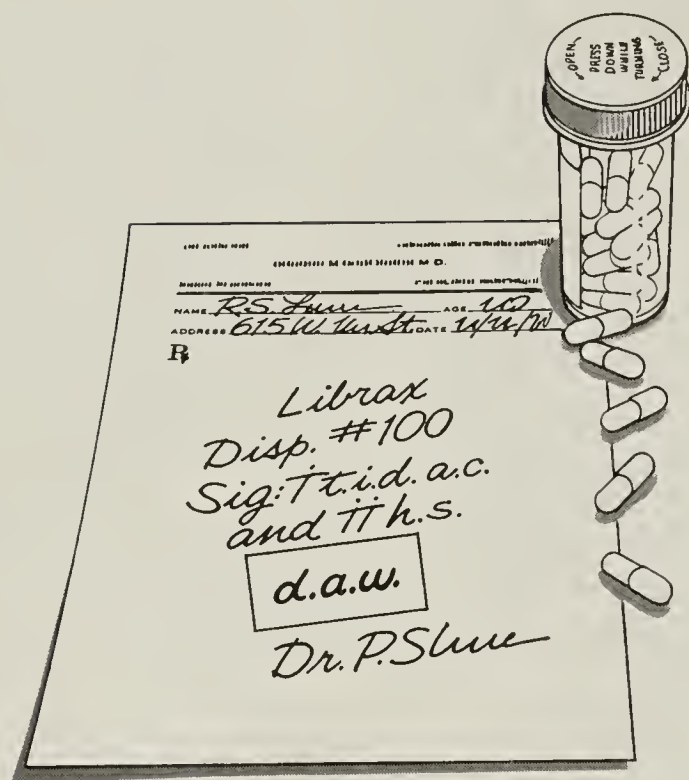
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Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur. Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such

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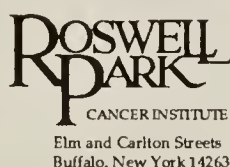
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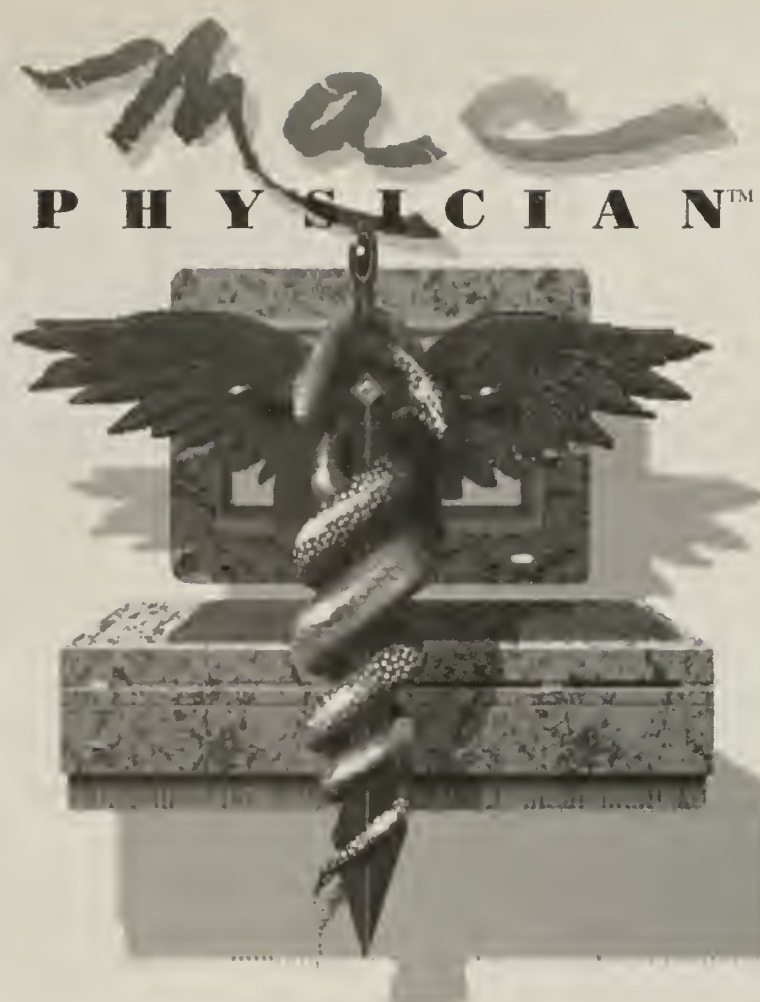
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What do
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HIV infection
have in common?



Diagnosis and treatment before symptoms develop can make a difference in a patient's life.

There's more than one way to identify patients at risk of HIV infection.

But the two most important ways are by taking a sexual history and a drug history of all your male and female patients. Asking the right questions in a nonjudgmental way is critical.

A patient's medical history can also hold clues. A history of genital herpes, syphilis, or other STDs may be an indication of at-risk behavior.

You should be aware of lab indicators that signal the possibility of HIV infection: unexplained anemia, increased LDH or serum globulin count, low serum cholesterol count, or idiopathic thrombocytopenic purpura.

And probe for early clinical signs, including recent occurrences of oral thrush, weight loss, perianal herpes, zoster, chronic vaginitis, and hairy leukoplakia.

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Reference: 1. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *N Engl J Med.* 1990;322:941-949.

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Microbiology: The development of resistance to zidovudine has not been adequately studied and the frequency of zidovudine-resistant isolates existing in the general population is unknown. Reduced *in vitro* sensitivity to zidovudine has been observed, however, in viral isolates from some individuals who have received prolonged courses of zidovudine treatment. For the small number of patients from whom isolates were studied, no correlations were evident between the development of reduced sensitivity in the laboratory and clinical response. Therefore, the quantitative relationship between *in vitro* susceptibility of HIV to zidovudine and clinical response to therapy has not been established. Studies of the development of resistance to zidovudine are incomplete and the frequency and degree of changes in *in vitro* sensitivity of virus isolates from HIV infected patients with differing severity of immune compromise are unknown.

INDICATIONS AND USAGE: Retrovir is indicated for the management of adult patients with HIV infection who have evidence of impaired immunity (CD4 cell count of 500/mm³ or less) before therapy is begun. Retrovir is also indicated for HIV-infected children over 3 months of age who have HIV-related symptoms or who are asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. These indications are based on the results of three randomized, double-blind, placebo-controlled trials of oral zidovudine in HIV-infected adult patients with CD4 cell counts of 500/mm³ or less, and two open-label studies involving 124 children ages 3.5 months to 12 years with advanced HIV-associated disease. Specifically, separate studies evaluated zidovudine therapy in asymptomatic HIV-infected adults, in adults with early symptomatic disease, in adults with advanced symptomatic HIV disease (AIDS or advanced ARC), and in children with advanced symptomatic HIV disease (pediatric AIDS or advanced ARC).

Adults Asymptomatic HIV Infection: A randomized, double-blind, placebo-controlled trial of oral zidovudine was conducted in asymptomatic, HIV-infected adults at 32 medical centers. Entry was dependent on the absence of signs and symptoms consistent with HIV disease, such as significant weight loss, fever, diarrhea, secondary infections and evidence of neurological dysfunction. In the study, 1338 asymptomatic individuals with absolute CD4 (T4) lymphocyte counts of less than 500 cells/mm³ received a regimen of either 100 mg zidovudine, 300 mg zidovudine, or placebo, each administered five times a day. These study participants were monitored for the development of signs and symptoms of HIV disease and tolerance to the study regimens. The study was terminated early because of a statistically significant difference in progression to advanced symptomatic HIV disease (AIDS or advanced ARC) between the 500 mg/day zidovudine group and the placebo group. Of the 1338 patients enrolled in the study, 38 of the 428 patients receiving placebo, 17 of the 453 individuals receiving 500 mg zidovudine, and 19 of the 457 recipients of 1500 mg zidovudine progressed to advanced symptomatic HIV disease when followed for a mean of 55 weeks (range 19-107 weeks). Of the progressions noted above, AIDS occurred in 33 placebo recipients, 11 individuals receiving 500 mg and 14 patients receiving 1500 mg zidovudine. Changes in immunologic and virologic parameters (ie, CD4 [T4] lymphocyte count and serum p24 antigen levels) paralleled the observed clinical benefits. Consistent with various epidemiologic studies of individuals with HIV infection, patients in this study with lower CD₄ cell counts or p24 antigenemia were more likely to progress to AIDS. Virtually all patients (for whom data are available) experienced a decline in CD₄ cell counts to less than 200 per mm³ before developing an AIDS-defining opportunistic infection. Although treatment of asymptomatic patients delays progression of disease in those patients at risk of progression over the initial 1-2 years of treatment, it is not known whether early treatment prolongs survival.

Zidovudine was well tolerated in a majority of patients. The following adverse clinical events were reported at a significantly greater incidence in individuals receiving 500 mg/day of zidovudine versus placebo: headache, malaise, anorexia, nausea and vomiting (see ADVERSE REACTIONS).

The two most common laboratory abnormalities reported were anemia and granulocytopenia, each of which occurred more often in patients receiving higher doses. These toxicities were easily managed in most cases by temporary dose interruption.

Early Symptomatic HIV Disease: This randomized, double-blind, placebo-controlled trial of oral zidovudine, conducted at 29 medical centers, studied 713 adults with early manifestations of HIV disease (ie, a baseline CD4 [T4] cell count of 200 to 800/mm³ and symptoms such as oral thrush, oral hairy leukoplakia or intermittent diarrhea). Patients received either placebo or 200 mg zidovudine every 4 hours (1200 mg/day). The trial was terminated early because of a statistically significant difference in the rates of development of advanced symptomatic HIV disease between the zidovudine and placebo groups. Of the 352 patients receiving placebo, 36 progressed to advanced symptomatic HIV disease, of whom 21 progressed to AIDS; whereas of the 361 zidovudine recipients, 13 progressed to advanced symptomatic HIV disease, of whom 5 progressed to AIDS.

Minimal toxicity was observed. Four percent of zidovudine recipients compared with none of the placebo recipients developed a hemoglobin concentration less than 8 g/dL and 4% of patients treated with zidovudine compared with 1% of placebo recipients developed a granulocyte count less than 750 cells/mm³. Asthenia, dyspepsia, nausea, and vomiting were the major adverse clinical events reported at significantly greater incidences in patients receiving zidovudine.

Advanced Symptomatic HIV Disease: This randomized, double-blind, placebo-controlled trial, conducted at 12 medical centers, was the original trial upon which the marketing of Retrovir was based. In this trial, 281 adults with advanced symptomatic HIV infection including AIDS were studied for a mean of four and a half months.

The patient population of this controlled trial consisted of 160 patients with AIDS (85 Retrovir and 75 placebo) who had recovered from their first episode of PCP diagnosed within the previous four months and 121 patients with ARC (59 Retrovir and 62 placebo) with multiple signs and symptoms of HIV infection, including mucocutaneous candidiasis and/or unexplained weight loss (≥ 15 lbs or $>10\%$ of prior body weight). All patients had evidence of impaired cellular immunity with an absence of delayed cutaneous hypersensitivity and CD4 (T4) lymphocytes less than 500 cells/mm³. All patients began therapy at a dose of 250 mg every 4 hours around the clock. This dosage was reduced or temporarily or permanently discontinued after serious marrow toxicity occurred. The trial was stopped early because of a statistically significant difference in mortality. There were 19 deaths in the placebo group and 1 in the Retrovir group. All deaths were apparently due to opportunistic infections (OI) or other complications of HIV infection. Treatment duration ranged from 12 weeks to 26 weeks, with a mean and median duration of 17 and 18 weeks, respectively.

Retrovir also significantly reduced the risk of acquiring an AIDS-defining OI in patients after 6 weeks of treatment. In addition, patients who received Retrovir generally did better than the placebo group in terms of several other measures of efficacy including performance level, neuropsychiatric function, maintenance of body weight and the number and severity of symptoms associated with HIV infection. A small, transient increase in mean CD4 (T4) counts was seen in the zidovudine group but the significance of this finding is unclear.

The most significant adverse reaction noted in the study was a depression of formed elements in the peripheral blood, which necessitated dose reduction or drug discontinuation in 34% of patients receiving Retrovir. Patients with lower CD4 counts were more likely to receive transfusions. 41% of Retrovir recipients and 16% of placebo recipients with <200 CD4 lymphocytes at entry were transfused (see ADVERSE REACTIONS). Only one of 30 Retrovir recipients and none of 30 placebo recipients with >200 CD4 lymphocytes required transfusion. Although mean platelet counts in Retrovir recipients were statistically increased compared to mean baseline values, thrombocytopenia did occur in some patients. Twelve percent (12%) of Retrovir recipients compared to 5% of placebo recipients had $>50\%$ decreases from baseline platelet count.

At the conclusion of the placebo-controlled trial, approximately 80% of Retrovir and placebo recipients elected to enroll in an uncontrolled extension protocol in which all patients received Retrovir at a dose of 200 mg every four hours. This dose was chosen because of concern about hematologic toxicity and to allow for greater flexibility in dosing. These patients have been followed for variable periods of time. As the follow-up period lengthened, patient tracking became increasingly difficult. The intended treatment period of the original study was six months; however, some follow-up data are available for over 90% of patients originally enrolled in the trial. Data from patients in this and other studies show no new or unexpected clinical or laboratory adverse experiences for patients receiving Retrovir other than those listed (see ADVERSE REACTIONS), nor have previously reported adverse events increased significantly in frequency or severity with prolonged drug administration. At any time on study, approximately half of the patients received the recommended dose of zidovudine, while the remaining patients required reduction or interruption of their dosage regimen in response to myelosuppression and/or other clinical adverse events.

Benefits of therapy with Retrovir were observed during this extended period, although opportunistic infections continued to occur and additional patients died. Survival for all patients originally randomized to receive Retrovir was 96.5% at six months, 84.7% at one year, 68.3% at 18 months and 41.2% at two years. One year and two year survival for patients who entered the trial with AIDS was 79% and 31% when calculated since initiation of therapy (87% and 43%, respectively, since the first diagnosis of PCP). These survival rates were determined by the "intention to treat" method, which assumes all patients assigned to a drug actually took the drug throughout the study period.

While a direct comparison with survival data from other cohorts is not possible, untreated adult patients with AIDS diagnosed in San Francisco in 1985 who had survived 60 days after PCP had a one year survival of 34.7% and a two year survival of 4.2%. From diagnosis of PCP. In a recent epidemiologic study of patients with AIDS diagnosed in San Francisco in 1986 and 1987, median survival was improved for patients receiving Retrovir compared to those not receiving therapy with Retrovir (21.6 vs 14.9 months). Actual survival of untreated patients is likely to be lower than reported because of the difficulty in complete ascertainment of mortality. Caution is advised in making comparisons from such "natural history" experience since case definitions and follow-up practices vary.

Other, uncontrolled studies have shown that Retrovir may be of benefit in treating women, intravenous drug users, and racial minorities, in addition to the patient population (primarily white males) included in the controlled trials.

Dose Comparison Study: Results from a randomized, unblinded, dose comparison study of zidovudine, in adults with AIDS who had experienced an episode of PCP, indicate that an induction dose of zidovudine 200 mg administered orally every four hours (1200 mg/day) for one month, followed by chronic administration of 100 mg every 4 hours (600 mg/day), was associated with survival rates and frequency of opportunistic infections comparable to those observed in patients administered higher dosages as tolerated. The 600 mg per day regime was also associated with a lower incidence of hematologic toxicity. The effectiveness of this lower dose in improving the neurologic dysfunction associated with HIV disease, however, is unknown (see DOSAGE AND ADMINISTRATION).

Pediatric Symptomatic HIV Disease: Two open-label studies have evaluated the pharmacokinetics, safety and efficacy of Retrovir in 124 children with advanced HIV disease (84 AIDS and 40 with other clinical and laboratory evidence of advanced HIV disease). The median age at entry was 3 years with 14% less than 12 months of age. In the majority of cases (73%), HIV was acquired by vertical transmission from an HIV-infected mother. Thirty-six children were enrolled in the Phase 1 study, which evaluated three intravenous dosing regimens administered for 4 to 8 weeks. All children subsequently switched to an oral dose of 180 mg/m² every 6 hours and were followed for a mean of 465 days (range 121 to 855 days). Eighty-eight children participated in the Phase 2 study and these children were monitored for a mean of 186 days (range 3 to 352 days). In the Phase 2 study, oral zidovudine was initiated at a dose of 180 mg/m² every 6 hours.

Clinical, immunologic and virologic improvements were observed among some of the children receiving zidovudine in these open-label studies. Clinical improvements included reductions in hepatosplenomegaly and increase in weight percentiles in previously growth retarded children. The probability of remaining free of opportunistic infections through 12 months of follow-up was 0.76. Thirty-seven children developed one or more documented serious bacterial infections while participating in the studies. Seven of these children had more than one documented serious bacterial infection. The probability of survival at 12 months is 0.87 for the 124 patients enrolled in the Phase 1 and Phase 2 studies.

Improvements in the immunologic parameters CD4 cell counts and immunoglobulin concentration were observed among the study participants. For children with severely depressed CD4 cell counts (<500 /mm³) at entry, mean increase of 148/mm³ in CD4 lymphocyte cell count was observed during the first two months of zidovudine therapy. Thereafter, CD4 cell counts declined but remained above baseline through 9 months of follow-up. A tendency towards normalization of elevated immunoglobulin concentrations (primarily IgG) was observed among study participants.

Substantial reductions in serum and CSF P₂₄ antigen concentrations were observed in some patients, as well as a reduction in the number of patients with positive CSF HIV cultures, providing evidence of anti-retroviral effect. The most frequently reported adverse events were anemia (Hgb <7.5 g/dL) and neutropenia (<750 /mm³) which occurred in forty-six percent of the children. Thirty-six percent of the patients had their dose modified due to the development of hematologic abnormalities and 30% received transfusions for anemia. Four patients had dosing permanently discontinued due to neutropenia (see ADVERSE REACTIONS).

CONTRAINDICATIONS: Retrovir Capsules and Syrup are contraindicated for patients who have potentially life threatening allergic reactions to any of the components of the formulations.

WARNINGS: Zidovudine has been studied in controlled trials in significant numbers of asymptomatic and symptomatic HIV infected patients, but only for limited periods of time. Therefore, the full safety and efficacy profile of zidovudine has not been defined, particularly in regard to prolonged use and especially in HIV infected individuals who have less advanced disease (see following sections for more specific information: INDICATIONS AND USAGE, Microbiology, Carcinogenesis, Mutagenesis, Impairment of Fertility).

Insufficient clinical experience exists to recommend a dosing regimen in infants under 3 months of age. Preliminary evidence indicates that zidovudine clearance may be reduced in children less than one month of age.

A positive test for HIV-antibody in children under 15 months of age may represent passively acquired maternal antibodies, rather than an active antibody response to infection in the infant. Thus, the presence of HIV antibody in a child less than 15 months of age must be interpreted with caution, especially in the asymptomatic infant. Confirmatory tests such as serum P₂₄ antigen or viral culture should be pursued in such children.

Zidovudine should be used with extreme caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 /mm³ or hemoglobin <9 g/dL. In all of the placebo-controlled studies, but most frequently in patients with advanced symptomatic HIV disease, anemia and granulocytopenia were the most significant adverse events observed (see ADVERSE REACTIONS). There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug. Significant anemia most commonly occurred after 4 to 6 weeks of therapy and in many cases required dose adjustment, discontinuation of zidovudine, and/or blood transfusions. Frequent blood counts are strongly recommended in patients with advanced HIV disease taking zidovudine. For asymptomatic HIV-infected individuals and patients with early HIV disease, most of whom have better marrow reserve, blood counts may be obtained less frequently, depending upon the patient's overall status. If anemia or granulocytopenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION in full prescribing information).

Sensitization reactions, including anaphylaxis in one patient, have been reported in individuals receiving zidovudine therapy. Patients experiencing a rash should undergo medical evaluation.

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated (see Drug Interactions under PRECAUTIONS). Zidovudine recipients who used acetaminophen during the controlled trial in advanced HIV disease, had an increased incidence of granulocytopenia which appeared to be correlated with the duration of acetaminophen use.

PRECAUTIONS:

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). There are currently very little data available concerning the use of zidovudine in patients with impaired renal function (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY) and no data in patients with impaired hepatic function. These patients may be at greater risk of toxicity from zidovudine.

Information for Patients: See full prescribing information.

Drug Interactions: The interaction of other drugs with zidovudine has not been studied in a systematic manner. Coadministration of zidovudine with drugs that are nephrotoxic, cytotoxic, or which interfere with RBC/WBC number or function (eg, dapson, pentamidine, amphotericin B, flucytosine, vincristine, vinblastine, adriamycin or interferon) may increase the risk of toxicity. Limited data suggest that probenecid may inhibit glucuronidation and/or reduce renal excretion of zidovudine. In addition, other drugs (eg, acetaminophen, aspirin, or in domethacin) may competitively inhibit glucuronidation (see WARNINGS). Phenytoin levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. These observations suggest that phenytoin levels should be carefully monitored in patients receiving zidovudine since many patients with advanced HIV infections have CNS conditions which may predispose to seizure activity.

Some experimental nucleoside analogues which are being evaluated in HIV-infected patients may affect RBC/WBC number or function and may increase the potential for hematologic toxicity of zidovudine. Some experimental nucleoside analogues affecting DNA replication antagonize the *in vitro* antiviral activity of zidovudine against HIV and thus, concomitant use of such drugs should be avoided.

Some drugs such as trimethoprim-sulfamethoxazole, pyrimethamine, and acyclovir may be necessary for the management or prevention of opportunistic infections. In the controlled trial, in patients with advanced HIV disease, increased toxicity was not detected with limited exposure to these drugs. However, there is one published report of neurotoxicity (profound lethargy) associated with concomitant use of zidovudine and acyclovir.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Zidovudine was administered orally at three dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60 and 120 mg/kg/day in mice and 80, 220 and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30 and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, one squamous cell papilloma and one squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle dose animal. No vaginal tumors were found at the lowest dose.

In rats, two late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats.

No other drug-related tumors were observed in either sex of either species.

It is not known how predictive the results of rodent carcinogenicity studies may be for man. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames *Salmonella* mutagenicity assay. In a mutagenicity assay conducted in L5178Y/TK⁺ mouse lymphoma cells, zidovudine

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as weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4000 and 5000 µg/mL). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations 1000 µg/mL and higher. In an *in vitro* mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 µg/mL and higher. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 µg/mL and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1 µg/mL. In an *in vivo* cytogenetic study in rats given a single intravenous injection of zidovudine at doses of 37.5 to 300 mg/kg, there were no treatment-related structural or numerical chromosomal alterations in spite of plasma levels that were as high as 453 µg/mL five minutes after dosing. In two *in vivo* micronucleus studies (designed to measure chromosome breakage or mitotic spindle apparatus damage) in male mice, oral doses of zidovudine of 100 to 1000 mg/kg/day administered once daily for approximately 4 weeks induced dose-related increases in micronucleated erythrocytes. Similar results were also seen after 4 or 7 days of dosing at 500 mg/kg/day in rats and mice. No effect on male or female fertility (judged by conception rates) was seen in rats given zidovudine orally at doses up to 450 mg/kg/day. **Pregnancy:** Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. The incidence of fetal resorptions was increased in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak plasma concentrations in rats of 68 to 234 times the peak human plasma concentrations and in rabbits 14 to 90 times the peak human plasma concentrations. It is not known whether zidovudine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Zidovudine should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether zidovudine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from zidovudine in nursing infants, mothers should be instructed to discontinue nursing if they are receiving zidovudine. **Pediatric Use:** See INDICATIONS and WARNINGS sections.

OVERSE REACTIONS: Adults: The frequency and severity of adverse events associated with the use of zidovudine in adults are greater in patients with more advanced infection at the time of initiation of therapy. The following tables summarize the relative incidence of hematologic adverse events observed in the placebo-controlled clinical studies by severity of HIV disease present at the start of treatment.

Asymptomatic HIV Infection Study (n=1338)	Granulocytopenia (<750/mm ³)		
	Zidovudine		Placebo
	1500 mg*	500 mg	
CD4 ≤ 500	6.4% (n=457)	1.8% (n=453)	1.6% (n=428)
Asymptomatic HIV Infection Study (n=1338)	Anemia (Hgb<8 g/dL)		
	Zidovudine		Placebo
	1500 mg*	500 mg	
CD4 ≤ 500	6.4% (n=457)	1.1% (n=453)	0.2% (n=428)

Early Symptomatic HIV Disease Study (n=713)	Granulocytopenia (<750/mm ³)		Anemia (Hgb<8 g/dL)	
	Zidovudine 1200 mg	Placebo	Zidovudine 1200 mg	Placebo
CD4>200	4%(n=361)	1%(n=352)	4%(n=361)	0%(n=352)

Advanced Symptomatic HIV Disease Study (n=281)	Granulocytopenia (<750/mm ³)		Anemia (Hgb<7.5 g/dL)	
	Zidovudine 1500 mg*		Placebo	
	Zidovudine 1500 mg*	Placebo	Zidovudine 1500 mg*	Placebo
CD4>200	10%(n=30)	3%(n=30)	3%(n=30)	0%(n=30)
CD4<200	47%(n=114)	10%(n=107)	29%(n=114)	5%(n=107)

*Three times the currently recommended dose in asymptomatic patients. The anemia reported in patients receiving zidovudine appeared to be the result of impaired erythrocyte maturation as evidenced by increased macrocytosis (MCV) while on drug. The HIV-infected adults participating in these clinical trials often had baseline symptoms and signs of HIV disease and/or experienced adverse events at some time during study. It was often difficult to distinguish adverse events possibly associated with zidovudine administration from underlying signs of HIV disease or intercurrent illnesses. The following table summarizes clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with zidovudine in the original placebo-controlled study. Of the items listed in the table, only severe headache, nausea, insomnia and myalgia were reported at a significantly greater rate in zidovudine recipients.

Percentage (%) of Patients with Clinical Events in the Advanced HIV Disease Study		
Adverse Event	Zidovudine (n=144) %	Placebo (n=137) %
BODY AS A WHOLE		
Asthenia	19	18
Diaphoresis	5	4
Fever	16	12
Headache	42	37
Malaise	8	7
GASTROINTESTINAL		
Anorexia	11	8
Diarrhea	12	18
Dyspepsia	5	4
GI Pain	20	19
Nausea	46	18
Vomiting	6	3
MUSCULOSKELETAL		
Myalgia	8	2
NERVOUS		
Dizziness	6	4
Insomnia	5	1
Paresthesia	6	3
Somnolence	8	9
RESPIRATORY		
Dyspnea	5	3
SKIN		
Rash	17	15
SPECIAL SENSES		
Taste Perversion	5	8

Clinical adverse events which occurred in less than 5% of all adult patients treated with zidovudine in the advanced HIV study are listed below. Since many of these adverse events were seen in placebo-treated patients as well as zidovudine recipients, their possible relationship to the drug is unknown.

Body as a whole: body odor, chills, edema of the lip, flu syndrome, hyperalgesia, back pain, chest pain, lymphadenopathy. **Cardiovascular:** vasodilation. **Gastrointestinal:** constipation, dysphagia, edema of the tongue, eructation, flatulence, bleeding gums, rectal hemorrhage, mouth ulcer. **Musculoskeletal:** arthralgia, muscle spasm, tremor, twitch. **Nervous:** anxiety, confusion, depression, emotional lability, nervousness, syncope, loss of mental acuity, vertigo.

Respiratory: cough, epistaxis, pharyngitis, rhinitis, sinusitis, hoarseness. **Skin:** acne, pruritus, urticaria. **Special senses:** amblyopia, hearing loss, photophobia. **Urogenital:** dysuria, polyuria, urinary frequency, urinary hesitancy.

Subsequent to the initial trial, myopathy and sensitization reactions, including anaphylaxis in one patient, have been reported in adults receiving zidovudine therapy.

All unexpected events and expected events of a severe or life-threatening nature were monitored for adults in the placebo-controlled studies in early HIV disease and asymptomatic HIV infection. Data concerning the occurrence of additional signs or symptoms were also collected. No distinction was made in reporting events between those possibly associated with the administration of the study medication and those due to the underlying disease. The following tables summarize all those events reported at a statistically significant greater incidence for zidovudine recipients in these studies.

Percentage (%) of Patients with Clinical Events in the Early Symptomatic HIV Disease Study		
Adverse Event	Zidovudine (n=361) %	Placebo (n=352) %
BODY AS A WHOLE		
Asthenia	69	62
GASTROINTESTINAL		
Dyspepsia	6	1
Nausea	61	41
Vomiting	25	13

Percentage (%) of Patients with Clinical Events* in an Asymptomatic HIV Infection Study			
Adverse Event	1500 mg Zidovudine*** (n=457) %	500 mg Zidovudine (n=453) %	Placebo (n=428) %
BODY AS A WHOLE			
Asthenia	10.1	8.6**	5.8
Headache	58.0**	62.5	52.6
Malaise	55.6	53.2	44.9
GASTROINTESTINAL			
Anorexia	19.3	20.1	10.5
Constipation	8.1	6.4**	3.5
Nausea	57.3	51.4	29.9
Vomiting	16.4	17.2	9.8
NERVOUS			
Dizziness	20.8	17.9**	15.2

*Reported in ≥ 5% of study population. **Not statistically significant versus placebo. ***Three times the currently recommended dose in asymptomatic patients. The following events have been reported in adult patients treated with zidovudine: seizures, nail pigmentation, changes in liver function tests. They may also occur as part of the underlying disease process. As such, the relationship between these events and the use of zidovudine is uncertain.

Pediatrics: The incidences of anemia and granulocytopenia among children with advanced HIV disease receiving zidovudine were similar to the incidences which have been reported for adults with AIDS or advanced ARC (see above). Management of neutropenia and anemia included, in some cases, dose modification and/or blood product transfusions. In the open-label studies, seventeen percent had their dose modified (generally a reduction in dose by 30%) due to anemia and 25% had their dose modified (temporary discontinuation or dose reduction by 30%) for neutropenia. Four children had zidovudine permanently discontinued for neutropenia. The following table summarizes the occurrence of anemia (Hgb < 7.5 g/dL) and granulocytopenia (<750/mm³) among 124 children receiving zidovudine for a mean of 267 days (range 3 to 855 days).

Advanced Pediatric HIV disease (N=124)	Granulocytopenia (<750/mm ³)		Anemia (Hgb < 7.5 g/dL)	
	N	%	N	%
	48	39	28*	23

*Twenty-two children received one or more transfusions due to a decline in hemoglobin to < 7.5 g/dL, an additional 15 children were transfused for hemoglobin levels > 7.5 g/dL. Fifty-nine percent of the patients transfused had a pre-study history of anemia or transfusion requirement. An increase in MCV (macrocytosis) was observed among the majority of children enrolled in the studies. In the open-label studies involving 124 children, 16 clinical adverse events were reported by 24 children. No event was reported by more than 5.6% of the study populations. Due to the open-label design of the studies, it was difficult to determine possible zidovudine-related versus disease-related events. Therefore, all clinical events reported as associated with zidovudine therapy or of unknown relationship to zidovudine therapy are presented in the following table:

Percentage (%) of Pediatric Patients with Clinical Events in Open Label Studies		
Adverse Event	N	%
BODY AS A WHOLE		
Fever	4	3.2
Phlebitis*/Bacteremia	2	1.6
Headache	2	1.6
GASTROINTESTINAL		
Nausea	1	0.8
Vomiting	6	4.8
Abdominal Pain	4	3.2
Diarrhea	1	0.8
Weight Loss	1	0.8
NERVOUS		
Insomnia	3	2.4
Nervousness/Irritability	2	1.6
Decreased Reflexes	7	5.6
Seizure	1	0.8
CARDIOVASCULAR		
Left Ventricular Dilation	1	0.8
Cardiomyopathy	1	0.8
S ₃ Gallop	1	0.8
Congestive Heart Failure	1	0.8
Generalized Edema	1	0.8
ECG Abnormality	3	2.4
UROGENITAL		
Hematuria/Viral Cystitis	1	0.8

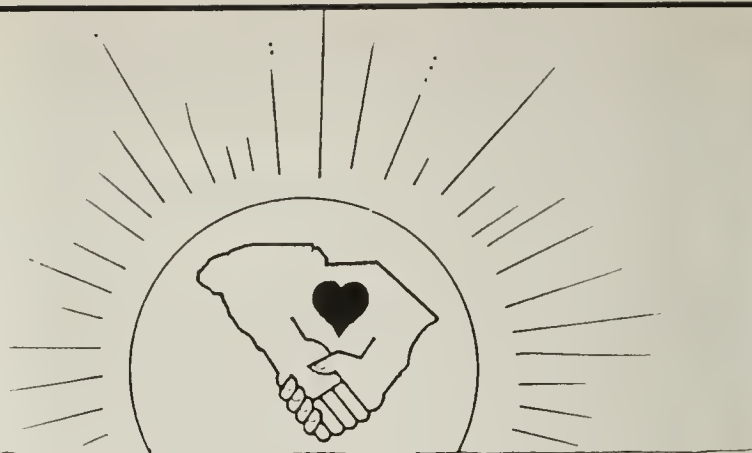
*Peripheral vein I.V. catheter site. The clinical adverse events reported among adult zidovudine recipients may also occur in children.



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MARCH 1991

AROUND THE STATE

MANHATTAN

Mar 1-3. NYU/Bellevue Hospital Center Psychiatry Board Review. 24 Cat I Credits. Mar 14-15. Stroke Prevention—Critical Assessment of Today's Strategies. 11½ Cat I Credits. Mar 16. Fiberoptic Endoscopy Workshop for the Management of the Difficult Airway. 8 Cat I Credits. Mar 17-22. Anesthesiology Comprehensive Review XI. 44 Cat I Credits. Waldorf Astoria Hotel. March

18-22. Seminar in Advanced Rheumatology. 25 Cat I Credits. Mar 22-23. Diagnostic and Operative Sinus Endoscopy. 13½ Cat I Credits. NYU Medical Center. Contact: NYU Medical Center, Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

Mar 11-12. 14th Perinatal Nurses Conference—In Search of the Perfect Baby. Marriot Marquis Hotel. Contact: Judith E. Steinhart, Director of Professional Education, March of Dimes, 233 Park Ave, New York, NY 10003. Tel: (212) 353-8353.

Mar 13-15. Advances in Cancer Treatment Research & Autologous Bone Marrow Transplant. 24 Cat I Credits. Grand Hyatt Hotel. Contact: Office of Continuing Medical Education, 3301 Bainbridge Ave, Bronx, NY 10467. Tel: (212) 920-06674.

Mar 21-23. 18th Annual Conference and Medical Research Symposium on Dyslexia. Penta Hotel. Contact: NY Branch of the Orton Dyslexia Society,

88 5th Ave, New York, NY 10011. Tel: (212) 691-1930.

STONY BROOK

Mar 23-27. 17th Annual Family Medicine Update. 37½ Cat I Credits. State University of New York at Stony Brook. Contact: Dorothy S. Lane, MD, Associate Dean for CME, School of Medicine, Health Science Center, 4L, Room 147, SUNY at Stony Brook, NY 11794. Tel: (516) 444-2094.

AROUND THE NATION

ARIZONA

Mar 25-29. Radiology Spring Training 1991. 24 Cat I Credits. Camelback Inn, Scottsdale. Contact: Radiology Postgraduate Education, Room C-324, University of California School of Medicine, San Francisco, CA 94143. Tel: (415) 476-5731.

(continued on p 18A)



COMMENTARIES

Responsibilities of health yuppies

Years ago, educated people who thought little of wealth but who passionately supported a variety of social causes were called "beatniks." These are the days of the "yuppie," the well-heeled, well-educated young professional who specializes in self-interest and egotism, with a penchant for mergers and acquisitions as well as designer ice cream.

As educated persons and health professionals, young physicians, or "health yuppies," may too easily lose sight of their appropriate goals and responsibilities. Their goals should include involvement with their families and commitment to their communities as well as to the medical profession. The term "family" encompasses both the traditional definition of immediate relatives and the more contemporary view of family as the extended, connected group of friends, neighbors, and others who share comparable life styles, interests, passions, concerns, and goals. "Community" can describe a tenants' groups, block association, neighborhood crime watch, or local parent-teacher association, as well as the historical preservation society, civic theater, teen recreation center, and houses of worship, for example.

However, there is another aspect of community, which entails looking anew at the surroundings and seeing and experiencing the hidden grim realities to which many of us have become inured. Profound poverty and complex social problems are present in our midst. Homeless people, sometimes entire families, are sleeping over grates on the sidewalks and in the parks. Alcohol-addicted and destitute men insist on wiping windshields as people fearfully drive through the Bowery. Young people struggle with their drug habits, teenagers are having babies, and many elderly people are barely surviving.

These people and these problems are also part of the community. These aspects of a young physician's community should not fade into the background as he or she aspires to and attains the professional and financial success associated with a "health yuppie." Too often, achieving a comfortable standard of living is accompanied by the loss of one's capacity to empathize with others, and a resultant complacency. Complacency among educated, talented

professionals can create a dangerous and pervasive social apathy and contribute to amorality throughout society.

As educated persons in a helping profession, young physicians are predominantly involved in service to the individual. However, a leadership role in the community at large is equally important. People give physicians their trust. They trust them with their health, and, in some cases, their ability to work. Physicians are placed on a pedestal in the community. Wearing a white jacket or uniform confers a certain status and is a mantle of respectability and professionalism. This status is not without its obligations, which extend beyond those of professional competency and preclude professional isolation. For example, when treating elderly patients, a physician must look beyond their obvious health problems and their aging eyes, to note as well their social isolation and the loneliness and disorientation that they may face. When providing professional care for the elderly, it is important to recognize that many of these people may be struggling with a fixed income, suffering from malnutrition, and facing needless deprivation because of inadequate public transportation. Some elderly patients may also experience the trauma of "warehousing" in nursing homes, being cared for by strangers and bewildered by rules and regulations and unwanted roommates.

Health yuppies have a responsibility to contribute their time and talents to the communities in which they make their homes and livelihoods, even in ways that may not be directly related to their careers. Young physicians and their families have much to gain personally by establishing ties to their communities, and, in the process, will enhance their professional standing. Every community benefits from the infusion of new values and new ideas.

Young health professionals may already be familiar with leadership through involvement in campus organizations, environmental groups, the antinuclear movement, or religious activities. As a health yuppie, these interests and activities should not be put aside. It is important to become involved, to get into the fray, and to take a stand in today's conflicts and problems.

By the turn of the century, just ten years hence, today's

health yuppies will have families and careers that are well established, and they will enter middle age in an era when older people are more productive and more vital than ever. By then, some of today's problems may be of crisis proportions. Who will help determine how our communities will deal with the homeless, the addicted, and with those afflicted with the acquired immunodeficiency syndrome (AIDS)?

The scope of these problems is already staggering. Consider the following examples. In the past ten years, the proportion of New York City residents classified as poor has soared from 17% to 25%.¹ Currently, more than 3,289 families and 12,000 single people in this city are homeless or are housed in hotels and shelters;² many of these makeshift residences are filthy and dangerous. Most of the children of these families are transferred from school to school and seem destined to be deprived of an education as well as of a stable home. An estimated 20-25% annual increase in homeless people is projected each year for several years to come.²

The illegal drug problem is epidemic. It is rampant in elementary schools, and it cries out from the sports pages of the newspapers. The introduction of crack cocaine to the drug scene has made an already dreadful cycle of addiction, dissolution, and crime even more deadly.

Nationwide, more than 67,300 people have already died of AIDS,³ and more than 15,700 of those deaths have been in New York City.⁴ Who will take care of, comfort, and house these terminally ill people awaiting medical miracles?

Accompanying this growing list of critical health and social problems is a crisis of leadership. There is corruption in government, on Wall Street, and even in the ministry. An ever-extending list of famous names gains a place on the dishonor roll. Health professionals and physicians are not immune from using the system for personal gain, corrupting their professions, and disavowing the values of their families, community, and profession. Immorality and irresponsibility are nothing new, but there seems today to be more and more emphasis on the hedonistic, the

"quick fix," instant gratification, and the philosophy of "take the money and run before getting caught."

At times, society appears to lack the leadership to combat countless, complex problems. However, there are many examples of people committed to change things for the better. It is important for those with means to give financial support to needy individuals, institutions, and causes, but writing a check is just part of the responsibility. Health professionals should also put a piece of themselves into the things they care about.

One only has to look around at relatives, friends, and neighbors, and see the dozens of examples of commitment and concern. Efforts are as varied as providing religious and moral education for children, organizing trips for terminally ill children, running for the school board, raising scholarship money through the Rotary Club, helping burned children through the Shriners, teaching cardiopulmonary resuscitation at the Red Cross, and working with the Association for the Help of Retarded Children.

Enjoyment of the good life should not displace one's capacity and determination to do good, to contribute, and to make a difference. There is great satisfaction and reward to be found by turning away from narcissism and embracing the causes that have meaning for oneself and for society.

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Spinal cord injuries in athletes

No other central nervous system injuries are more devastating and dramatic than those of the spinal cord in athletes. Despite the 1976 adoption of rules limiting initial player contact with the helmet,¹ there are still approximately a dozen such injuries annually in football in the United States, most of them due to use of the head in tackling.² Improper technique results in the player's striking his opponent with the head down, causing a hyperflexion or axial force to be transmitted to the cervical spine.

Athletic spinal injuries usually occur in the cervical spine and most commonly in the contact sports including football and wrestling. Gymnasts may sustain spinal injuries in falls suffered during dismounts. There are also spi-

nal injuries which occur during recreational, nonorganized activities such as diving, trampolining, skiing, surfing, and others. Of this group, diving injuries are the most common, constituting roughly 10% of all spinal cord injuries. These spinal injuries usually involve the mid-cervical area and are associated with neurological deficit in the majority of patients.

In the athlete with proven spinal cord and/or vertebral column injury, treatment is instituted along lines of conventional therapy. There are athletes, however, in whom symptoms are transient and associated with normal neurological and radiological examinations. These transiently injured patients often represent a dilemma with regard to

allowing return to participation in contact sports. When there is bilaterality of symptoms or involvement of one side of the body (arm and leg) or all four extremities, spinal cord injury is suggested. This is in contrast to the so-called "burner" or "stinger" injury, which is believed to be due to traction on the upper trunk of the brachial plexus. This is usually produced with the neck laterally flexed to the opposite side and a blow causing depression of the ipsilateral shoulder. There results a unilateral burning or dysesthetic pain in the fifth and sixth cervical dermatomes, normal neurological and radiological examinations, and spontaneous resolution of symptoms within several days to weeks. These injuries are common, being reported in up to one half of collegiate players during the course of a single season. The discernment of brachial plexus versus spinal cord involvement is an important factor not only in the initial management of athletes but also in prognostication for return to activity. The ultimate decision to allow an athlete with a suspected transient spinal cord injury to return to contact sport participation is difficult and must be done on an individual basis.

The article in this issue of the *Journal* by Marzo et al³ is a detailed analysis of cervical injuries during two high school football seasons. Although no catastrophic spinal cord injury occurred, eight individuals sustained cervical spine or brachial plexus injuries. Most occurred during the course of tackling, a well-appreciated phenomenon. This study emphasizes the importance of close surveil-

lance and documentation of injury in high school athletes, where 10% sustained some form of cervical involvement. It also emphasizes the inability of either a normal or abnormal medical history or physical examination to predict risk of subsequent injury.

Although progress has been made in the prevention of major cervical injuries in athletes, a high degree of diligence is constantly required. This fact is reiterated by the report of four cervical spinal cord injuries in football players in Louisiana for the 1989 season alone, a state in which the expected injury rate would be one for every 14 years.⁴ Like diving injuries, football mishaps are often preventable and public and professional awareness is necessary.⁵

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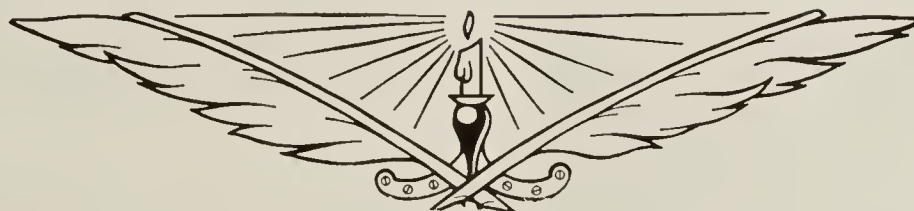
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Neck injuries to high school football players in Western New York State

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ABSTRACT. The goals of this study were to document the incidence of all injuries to the cervical spine at four Western New York high schools over two consecutive football seasons, and to compare the regional incidence to other reports. We also sought to identify the athletes at greatest risk of injury as determined by preseason questionnaire, medical history, and physical examination. Seventy-four high school football players entered the study prior to their junior season of play, and were followed prospectively for any reportable injury to the cervical spine.

An overall 10.8% rate of injury occurred over the two-year study period; the highest rate was for defensive backs and linebackers making a tackle. Thirty-two percent of players had an abnormal history, examination, or both prior to the first season of play. The medical community has a responsibility to educate the public concerning cervical spine injuries in high school football players.

(NY State J Med 1991; 91:46-49)

The orthopedic and neurosurgical communities began investigating serious and fatal head and neck football injuries after a report by Schneider¹ documented 78 neck injuries between 1959 and 1963. In another study, by Albright et al,² 32% of freshman college recruits at a major university had radiographic evidence of previous neck injury. Data from Torg et al,³ compiled through the National Football Head and Neck Injury Registry at the University of Pennsylvania, led directly to rule changes governing methods of tackle and play at the collegiate and interscholastic levels. Enforced in 1976, these changes dramatically decreased the number of serious head and neck injuries as reported by both Torg et al⁴ and Mueller and Blyth.⁵ In these studies, the number of cases of quadriplegia fell from 34 in 1976 to a low of five cases in 1984.

With the current emphasis on improving the size and strength of high school football players, and the increasing intensity with which the game is played, many young athletes are exposed to serious injury. In fact, Cantu et al⁶ report that football was responsible for 72% of all catastrophic injuries in high school sports from 1982 to 1987. Torg et al⁷ show that injury to the head and neck accounts

for the majority of catastrophic football injuries. Injury to the cervical spine may be particularly devastating, as the cervical spinal cord is incapable of regeneration. Prevention should be a primary concern of players, coaches, physicians, parents, and school officials.

Other types of injury, including "stingers" or "burners" and cervical strains, have received much less attention, and their incidence is not well documented. Possibly, there is gross underreporting of these types of injury due to a lack of interest, poor recordkeeping, and fear of time lost from play.

The goals of the study were to document the incidence of all injuries to the cervical spine at four Western New York State high schools over two consecutive seasons, and to compare the regional incidence to other reports. An attempt was made to identify the athlete at risk of injury as determined by preseason questionnaire, history, and physical examination. A recent study by Tucker et al⁸ revealed that 68% of the personnel responsible for medical coverage of high school football players in New York State are family practitioners and pediatricians, and it is important that they be familiar with these issues.

METHODS

Prior to the start of the 1987 Western New York high school football season, 74 athletes were interviewed, and they completed a questionnaire to determine prior history of neck injury. The players also had a complete cervical spine examination, including a neurologic examination of the upper extremities. The questionnaire and interview were designed to detect any history of previous injury, including strains or sprains, stingers or burners, fractures, dislocations, or temporary neurologic syndromes. Height, weight, and position on the roster were also documented.

The history was regarded as positive if any of the ten prompting questions was affirmatively answered, and a detailed interview pertaining to that question was carried out. The physical examination was considered abnormal if there was any tenderness on palpation; limited range of motion; sensory, motor, or reflex changes; or a positive compression test.

Initially, as part of the physical examination, lateral and flexion-extension radiographs were desired on all the participants. Parents were provided with information regarding the goals of the study and the importance of radiographs in meeting these goals. The coaches and athletic directors were provided a copy of the study protocol, and special arrangements were made for each school to have radiographs completed on a separate evening after practice. Despite this, and to our disappointment, only one athlete reported radiographic evaluation.

All practices and games were covered by an athletic trainer. A reportable injury was defined as any injury significant enough to

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be brought to the trainer's attention. Each injury was recorded on a standard form by the athletic trainer, documenting mechanism of injury, complaints, and results of the initial examination. Any player forced to miss a single practice or game was referred to the principal investigator for further evaluation. Each injury was recorded by the physician, documenting the results of an examination, routine radiographs, and any other diagnostic tests used, such as computed tomography, magnetic resonance imaging, and myelography. A diagnosis was reached, and the treatment plan begun. The athlete was returned to competition only after diagnostic tests were negative, symptoms were relieved, and the examination results had returned to normal. The total number of days lost from play were documented.

RESULTS

History and Physical. A history of injury was obtained from 16

of 74 varsity high school football players prior to the 1987 season (Table I). Three of these 16 had had more than one episode of a neck problem. Nine players reported a previous injury from football, two from an awkward sleeping posture, and one each from gymnastics, wrestling, basketball, and a bicycling accident. One player had had three separate stinger injuries, but "could not recall" the exact circumstances of these episodes.

Ten players were considered to have an abnormal examination (Table II). Eight of these were on the basis of a subjectively limited range of motion, one with atrophy of the right sternocleidomastoid muscle, and one with a decreased left biceps reflex.

Two players had both an abnormal history and physical examination.

Injuries. During the two seasons of this study, eight injuries were reported (Table III). Six players had strain syndromes that resulted in minimal time lost from play in each case. One player

TABLE I. Abnormal Histories Obtained from 16 of 74 Athletes Prior to Study as Determined by a Detailed Questionnaire

School	Subject	Diagnosis as Recalled by Player	Activity That Caused Injury
1	1	Sprain	Football
	2	Stinger	Football
	3	Stinger (3 episodes)	Unknown
	4	Sprain	Wrestling
	5	Stiff neck (2 episodes)	Sleeping posture
2	1	Stiff neck	Football
	2	Stinger (3 episodes)	Football
	3	Neck pain	Football
		Stinger	Football
3	1	Stinger	Basketball
	2	Neck pain	Gymnastics
	3	Stinger	Sleeping posture
4	1	Stinger	Bicycle accident
	2	Stiff neck	Football
	3	Stinger	Football
	4	Neck pain	Football

TABLE II. Results of Abnormal Physical Examinations on 10 of 74 Players Prior to Study

School	Subject	Finding	History of Injury
1	1	Subjective decreased range of motion	yes
2	1	Subjective decreased range of motion	no
	2	Subjective decreased range of motion, and decreased left biceps reflex	no
3	1	Decreased left biceps reflex	no
	2	Subjective decreased range of motion	no
	3	Subjective decreased range of motion	no
	4	Asymmetrical biceps reflexes	no
	5	Subjective decreased range of motion	no
4	1	Atrophy of right sternocleidomastoid muscle	no
	2	Decreased left biceps reflex	yes

TABLE III. Summary of Documented Injuries to 8 of 74 Players Over Two Consecutive Playing Seasons

Player	Position	Mechanism of Injury	Diagnosis	Days Lost
1987				
a	Defensive back	Tackling, direct impact with helmet, neck flexed	Strain	0
b	Quarterback	Noncontact, overuse	Strain	0
c	Linebacker	Tackling, direct impact with helmet, neck flexed	Strain	3
d	Linebacker	Tackling, hit in left neck, forced left bend	Stinger	10
1988				
a	Kick returner	Tackled, struck in right neck with helmet	Neuropraxia	Season
b	Defensive back	Tackling, direct impact with helmet, right bend	Strain	2
c	Linebacker	Tackling, direct impact with helmet, neck flexed	Strain	2
d	Offensive center	Blocking, multiple direct impacts, neck neutral	Strain	7

sustained a typical stinger injury that resulted in ten days of lost playing time. Another player had an episode of transient neuropraxia which ended his playing season in compliance with the recommendation of his private neurologist. No player with an abnormal history or physical examination sustained a reportable injury.

Regarding mechanism of injury, five players were injured while making tackles from the defensive back or linebacker position. One player, a center, recalled multiple direct helmet-on-helmet contacts with his neck in neutral as he prepared to block the opposing nose tackle. The player with a neuropraxia was a ball carrier struck in the right anterolateral neck with the tackler's helmet. A quarterback with a cervical strain could not recall any specific mechanism of injury.

No player was identified with more than one injury during the two seasons of study.

DISCUSSION

Incidence of Injury. One of the first to focus attention on neck injuries in football players was Alley,⁹ who reported his results in 1964. He retrospectively studied 19,413 high school football players from southern California during the 1961 playing season. Of these, 118 suffered some type of neck injury. Ninety-five percent of these were cervical strain or sprain; the remaining 5.1% suffered a fracture. A case study of each injury revealed that 56% of cases violated a fundamental rule of play: "their heads were down and necks were flexed" during contact. In addition, 81% of injuries occurred in players who had undergone conditioning for less than seven days prior to injury. Alley recommended a longer preseason period of conditioning, and called for an examination of the technique of "spearing."

A 1973 high school coaches' questionnaire designed by Albright et al² revealed a 1.2% incidence of neck injury in 20,189 players. The rate of injury did not vary with school size, conference of play, or season record. Again, in this study, linebackers and defensive backs were at greatest risk of injury. The re-injury rate in the same season was 17.2%, suggesting that once a injury takes place, the athlete is at greater risk of re-injury. In a separate, prospective study of 342 college football players, Albright et al¹⁰ reported a 10.5% incidence of noncatastrophic injuries from 1978 to 1984. Importantly, 42% of these players had a subsequent injury at some time during their college career, and once a second injury occurred, 67% had a third injury. In a study by Andrish et al¹¹ a college player who had a neck injury was about five times more likely to sustain another injury than one who had never before had a neck sprain. These findings seem to substantiate the suspicion that there may be a cumulative effect of noncatastrophic neck injuries.

The incidence of neck injury in the current study is similar to the national incidence reported in the literature. In the current study, 10.8% of players followed for two years sustained a neck injury significant enough for them to miss a practice or game. This is the same injury rate as that reported by Albright et al,¹⁰ and most likely reflects an increased sensitivity in reporting injuries, and the prospective nature of both studies. Fortunately, we recorded no serious cervical spine injuries, but cautiously state that this is probably a reflection of the limited number of athletes studied during a relatively short period of time. Nearly two thirds of the reported injuries occurred in defensive backs or linebackers while making a tackle, and

this agrees with all previous reports. The occurrence of injury did not represent an increased risk of future injury in the study presented here, but this is in contrast to previous larger studies, in which injury represented a significant predictor of future injury in college football players. Again, our study is a limited, two-year report.

Players at risk. Another goal of this study was to identify players at increased risk of injury. In the 1976 report by Albright et al,² a surprising 32% of college freshmen recruits had radiographic evidence of prior cervical spine injury. The authors found that a normal preseason examination was not a reliable indicator of past injury, but an abnormal examination correlated with a 50% incidence of abnormal radiographic findings. This led to the conclusion that radiographs should remain a keystone to the screening examination, at least at the collegiate level. Prospective data collected by Albright et al¹⁰ revealed that evidence of past injury on physical examination by history, or on the basis of radiographic findings, predicted a two-fold increase in the risk of injury in 342 college players studied. Those players with an abnormal screening examination experienced a 13.5% injury rate, compared to a 7.0% rate in their normal counterparts. Another significant finding was that those with a higher degree of abnormality on the screening examination were prone to more severe injury when it occurred. Andrish et al¹¹ reported a 24.4% incidence of neck injury in college players with a history of neck injury, compared to only 7.8% in those without a history of neck injury.

An abnormal history or physical examination in the high school players described here did not predict an increase in risk of injury during the limited time of study. In contrast to other, larger studies, this points to the difficulty, from a practical point of view, in identifying the athlete at risk. It is important to note that a normal history or physical examination did not predict freedom from risk of injury. Unfortunately, we were unable to obtain preseason radiographs and cannot comment on this aspect of the evaluation. This points to a prevailing laissez-faire attitude on the part of what we feel are typical young athletes, parents, and coaches. This must be countered by concern from the medical community at large.

Acknowledgments. The authors thank the athletic trainers covering their school teams as part of their graduate athletic training curriculum. Without the careful monitoring of practices and games by these individuals, this project could not have been completed. We also appreciate the cooperation of the athletic directors, coaches, and players at the schools involved in this study.

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Rural medicine and the closed society

Pregnancy outcomes among Amish and non-Amish women

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ABSTRACT. A rural family practitioner may be responsible for the general medical and obstetric needs of a closed population such as the Old Order Amish. Until recently, the Amish in southern New York State have preferred to receive obstetric care in the home from traditional Amish midwives. Acceptance of prenatal care and hospital deliveries by rural physicians appears to be increasingly frequent among Amish primiparas in southern New York State, while non-Amish in the area have been seeking these services for decades regardless of parity. This retrospective chart review examines first pregnancy outcomes of Amish (N = 39) and non-Amish (N = 145) women who delivered their babies at a rural hospital in southern New York State during a four-year period. Little difference was found between the two groups of women regarding the overall good health of their first babies. In the Amish population there was less variability in maternal age, season in which the birth occurred, labor duration, and birth weight of babies. The Amish had their first child an average of one year later than the non-Amish. While research on a larger sample will be necessary to fully explore Amish vs non-Amish variances, this study demonstrates the effect that traditions and customs of a closed society such as the Amish may have on obstetric practice.

(NY State J Med 1991; 91:49-52)

Since 1980, family practitioners from the Tri-County Family Health Center, a rural practice in Cattaraugus County, New York, have provided general medical and obstetric care to an increasing segment of the Old Order Amish. To date, few descriptive studies have been published on Amish health; even fewer compare pregnancy outcomes of the Old Order Amish with the non-Amish.¹⁻⁷ This paper compares first pregnancies among a sample of Old Order Amish (hereinafter also referred to as Amish) women with non-Amish women from the Cattaraugus practice.

The Old Order Amish originated in Switzerland in 1693 as an offshoot of the Swiss Anabaptist, or Menno-

nite, movement of the 1500s. They began immigrating to America around 1714 and today number over 75,000, with approximately 3,000 living in western New York State.¹⁻³

The Amish today represent a relatively homogeneous population, which differs markedly from the "average" US population with respect to a number of life style factors. Some of these factors may be expected to affect pregnancy outcomes: arranged marriages, inbreeding, rural location, and farming occupations. The Amish have a strong societal and parental disapproval of promiscuity and the birth of children outside of wedlock; this may explain why venereal disease and cervical cancer are rare in their communities.⁴ The Amish have a high birth rate and, in 1986, the average number of live births per Amish family was approximately seven, compared with 3.27 for other farm families in the United States.³ Furthermore, the Amish forbid birth control and abortion. Although smoking is sometimes practiced by Amish men, the Amish generally do not consume alcohol or smoke cigarettes.^{1,3}

The Amish usually do not have physicians drawn from their own religious group.³ First babies are sometimes born in hospitals, but more often the Amish prefer to have subsequent births at home. A study of 100 married Amish women in Pennsylvania showed that of 472 pregnancies, 90% of first births, but only 59% of their most recent births, occurred in hospitals.² Twenty-two percent of the 100 women did not seek prenatal care until the sixth month of pregnancy.³

The Amish do not proselytize, and almost no new converts have been added to the groups since immigration.¹ There are approximately a dozen genetic disorders found in the Amish due to inbreeding, including cartilage-hair hypoplasia and six-fingered dwarfism.⁶

In consideration of the strong tenets and simple life style of the Amish, the main purpose of this study was to compare pregnancy outcomes between Amish and non-Amish women for variations that may be related to life style differences. Our hypothesis suggested differences in birth outcome between 39 Amish and 145 non-Amish first births, including significantly higher birth weight, gestational age, and Apgar scores at 1 and 5 minutes in the Amish group. The hypothesis was based on life style differences between the groups, particularly the prohibitions

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against smoking and alcohol use by Amish women. Our hypothesis included the belief that the Amish would have a significantly shorter labor duration because they may be more physically fit than their rural neighbors, due to less mechanization.

METHODS

The study examined first pregnancies of 39 Amish and 145 non-Amish women who delivered at Tri-County Memorial Hospital in Cattaraugus County, NY, during the calendar years 1983–1986. First pregnancies were chosen in order to increase the concordance between the non-Amish and Amish groups and because of the generally higher rate of complications noted in first pregnancies.¹⁰

All the women included in this study resided in rural Cattaraugus County, where the major occupations are manufacturing, health care services, and agriculture. The median income for 1981 in Cattaraugus County was \$14,140, while the mean income was \$16,135.¹¹ Information on the average income of the Amish is not available because the Amish do not pay taxes and do not share their income information with the public. Socioeconomic status could not be controlled for in this study due to the lack of information on patient income in hospital and office charts and the general lack of income information for the Amish.

The patient sample was drawn from the obstetrics log book at Tri-County Hospital. All Amish first births and a sample of every other non-Amish first birth were selected from the 289 primiparas delivered at the hospital during the calendar years 1983–1986. The Amish and non-Amish were identified by the specification of religion in the hospital obstetrics log. The non-Amish subgroup consisted of white women who practice a religion other than Amish or who practice no religion at all. Stillbirths and spontaneous abortions were included. No voluntary terminations of pregnancy were identified in the chart review.

For all primiparas, the prenatal records contained in the office charts of the practitioners were individually reviewed. Pertinent information was transferred to a data booklet. Pregnancy outcomes that were collected from the log book and verified by the charts included infant birth weight, gestational age, Apgar scores at 1 and 5 minutes, and labor duration. Information regarding the mother's religion, smoking during pregnancy, and alcohol or drug use during pregnancy was collected from the charts; while birth date of the infant, gender of the infant, and maternal age and weight at delivery were collected from the log book and verified by chart information. Maternal diabetes mellitus, maternal hypertension, maternal thrombophlebitis, maternal herpes, uterine bleeding, severe pre-eclampsia, premature rupture of membranes, and low/falling estriols were also noted from charts.

Three physicians attended almost all of the births at the hospital during this four-year period: a private obstetrician who worked at Tri-County Memorial Hospital, and two family physicians from the Tri-County Family Medicine Group. Whenever possible, the prenatal record in the office chart of the practitioner was reviewed in order to validate information noted in the prenatal record summary in the hospital obstetrics log book. The hospital obstetrics log book was utilized to obtain data on 56 cases for which office and hospital charts were unavailable. The log book contained information about all variables related to delivery but lacked data on maternal smoking, maternal alcohol use, and complications. It is likely that some of the 56 unavailable charts were those of patients transferred to another hospital with early signs of high risk pregnancy.

Smoking or alcohol use during pregnancy was indicated by a "yes" or "no" response. The frequency of cigarette or alcohol use, or information about illicit drug use, was not documented in the obstetrics log or office charts. Head circumference and body length measurements were not included in the analysis because of inconsistent documentation. Two multiple births were excluded because, on average, multiple birth infants have lower birth weights than single birth infants.¹²

The Statistical Package for the Social Sciences (SPSS-X) was utilized to analyze the data.⁹ A two-tailed t-test was used for comparison of means, and chi-square test with Yate's correction for comparison of proportions. Multiple linear regression was used to assess the contribution of the independent variables to the variation of the dependent variables (pregnancy outcomes), after adjusting for maternal age and infant gender.

RESULTS

Among first births analyzed, 39 were Amish and 145 were non-Amish. The distribution of all births is shown in Table I. There were no indications of mutations or genetic complications. Chi-square analysis showed no significant difference regarding infant gender: 23 (59%) of Amish infants and 72 (50%) of non-Amish infants were male ($p = 0.39$).

As shown in Table II, no significant intergroup difference in the physician attending at birth was revealed using chi-square analysis ($p = 0.35$). Amish and non-Amish women were equally likely to have been attended by an obstetrician, with more than 50% of the women in each group having a family physician present at the birth of their first child. Twenty-six (67%) of the Amish first babies were delivered by one of the two family physicians, 10 (26%) were delivered by an obstetrician, and 3 (8%) were delivered by a team including one of the family physicians and the Tri-County obstetrician. The family practitioners delivered 80 (55%) of the non-Amish babies, while 44 (30%) were delivered by the obstetrician, and 21 (15%) by the team.

No significant difference in mean maternal age was shown by t-test comparison ($p = 0.095$). Chi-square analysis revealed significantly fewer Amish women than non-Amish women under the age of 20 (Table II).

Information on maternal smoking and alcohol use during pregnancy was available for 39 (100%) of the Amish women and for 90 (62%) non-Amish (Table II). None of the Amish smoked; one third of the non-Amish did. The results of this comparison using chi-square analysis were significant ($p < 0.001$). Information on maternal alcohol use during pregnancy showed that no Amish mothers reported drinking alcohol during pregnancy, while six non-Amish mothers reported drinking during pregnancy. The number of those who did drink alcohol was too small to make a valid chi-square comparison (Table II).

Cesarean sections were performed on four (10%) of the Amish and 33 (23%) of the non-Amish mothers mainly due to a drop in fetal heart rate or to meconium-stained amniotic fluid. This difference was not statistically significant using chi-square analysis ($p = 0.13$).

Labor was induced in 8% of each group (three Amish and 11 non-Amish). As shown in Table II, chi-square analysis revealed no significant association regarding labor induction among the Amish and non-Amish ($p = 1.0$).

There were 31 valid observations of labor duration for Amish, 104 for non-Amish. We excluded 4 (10%) Amish and 33 (23%) non-Amish mothers who had cesarean sections and 3 (1%) Amish and 11 (8%) non-Amish in whom labor had been induced with oxytocin. Five of the non-Amish had had both induced labor and a cesarean section. We analyzed the labors of these 24 Amish and 65 non-Amish based on two categories of duration (Table II). The intergroup comparison of the proportion of labor duration less than ten hours was not statistically significant using a chi-square test ($p = 2.86$). However, a t-test revealed that mean labor duration for the Amish and non-Amish was significantly different, seven and ten hours, respectively ($p < 0.001$).

As Table III illustrates, comparisons of the proportion with birth weights $\geq 3,400$ g (7.5 lbs) using chi-square analysis showed a statistically significant difference between the groups ($p = 0.015$): 36% of Amish babies and 60% of non-Amish babies were $\geq 3,400$ g. Mean differences in newborn birth weight were not significant, as shown by t-test analysis ($p = 0.385$). Mean birth weights were 3,351.9 g (7 lbs 4 oz) and 3,428.3 g (7 lbs 6 oz) for Amish and non-Amish, respectively. Birth weights ranged from 2,610.5 g to 4,086 g and 823 g to 4,171 g for the Amish and non-Amish, respectively.

Chi-square analysis demonstrated no significant difference in gestational age when divided into two categories ($p = 0.73$). One

TABLE I. Number of Births at Tri-County Memorial Hospital, Cattaraugus County, NY, 1983-1986

Year	First Births		Total	All Births	
	Amish	Non-Amish		Birth	Total
1983	7	80	87	170	257
1984	10	79	89	180	269
1985	5	70	75	190	265
1986	17	63	80	200	280
Total	39	292	331	740	1,071

Amish infant (3%) and 8 non-Amish infants (6%) were premature. A t-test comparison of mean gestational age revealed no significant difference ($p = 0.902$), as mean age for both Amish and non-Amish infants was 39.9 weeks (Table III). The range of gestational ages for Amish infants was 36-42 weeks, 29.5-43 weeks for non-Amish infants.

Apgar 1 and 5 minute scores were divided into three categories: 0-6, infants possibly at risk; 7-8, good; and 9-10, very healthy. Apgar scores at one minute for three (8%) of the Amish infants and 17 (12%) of the non-Amish infants were rated in the 0-6 category; 23 (59%) Amish and 73 (50%) non-Amish in the 7-8 category, and 13 (33%) Amish and 55 (38%) non-Amish in the 9-10 category. There were no significant differences shown by chi-square analysis in Apgar scores at one minute ($p = 0.58$), or Apgar scores at five minutes ($p = 0.68$). T-test comparison revealed no significant difference regarding mean Apgar scores between groups ($p = 0.75$). No significant difference in mean Apgar scores at five minutes between groups was shown by t-test comparisons ($p = 0.88$) (Table III).

Amish and non-Amish were significantly different with regard to season at birth, as revealed in chi-square analysis (Table II). Amish were more likely to have their children in the fall, while distribution of non-Amish births was spaced throughout the year.

We utilized multiple linear regression to determine whether significant differences existed between the groups in each variable: birth weight, gestational age, Apgar 1 score, and Apgar 5 score, after controlling for variables known to affect birth outcome. The

variables controlled for included infant gender, maternal smoking, alcohol use, and age. The adjustment did not alter the results seen in the bivariate analyses.

DISCUSSION

The results of this study demonstrate little difference between Amish women and non-Amish women managed at the Tri-County Family Health Center with regard to first pregnancies. In general, there was more homogeneity in the Amish than the non-Amish population. Although means were similar for most measures, the range was narrower in general for the more socially and genetically restricted Amish population. Amish women appear to have their first babies at a later age and appear to have a shorter labor duration than the non-Amish.

The non-Amish had a wider range of maternal ages than the Amish, with proportionately more teenage pregnancies and pregnancies after the age of 30 in the non-Amish, while the Amish tended to have their first babies in their 20s. The Amish are not considered eligible to marry until after they become church members at the age of 18, and there were no unmarried Amish in the sample.

There were significant differences in labor duration; non-Amish had a mean almost three hours longer than the Amish. In the multivariate analysis this difference was explained by maternal age and gender of the infant. There was a wider distribution of labor duration in the non-Amish, though bias may have been introduced by the unavailability of data for some of the non-Amish.

There was no statistically significant difference between groups in the rate of cesarean sections. The 10% rate in the Amish may be considered low, while the 23%

TABLE II. Comparison of Amish and Non-Amish Births for Selected Risk Characteristics (Chi-square and t-test Analysis)

Characteristic	Amish (N = 39)	Non-Amish (N = 145)	p Value
Sex (% male)	59.0	49.7	NS
Maternal age in years (mean $\pm$ SD)	22.0 $\pm$ 1.8	21.0 $\pm$ 3.9	NS
($p < 20$)	5.1	42.1	<0.001
Maternal smoking* (%)	0.0	33.3	<0.001
Maternal alcohol use* (%)	0.0	5.5	†
Season (% fall)	56.4	20.7	<0.001
(% winter)	23.1	29.0	NS
(% spring)	10.2	29.7	<0.025
(% summer)	10.3	20.6	NS
Primary provider (% obstetrician)	23.1	32.4	NS
Attending at birth (% obstetrician only)	25.6	30.3	NS
(% obstetrician & family physician)	7.7	14.5	NS
Cesarean section (%)	10.3	22.8	NS
Induced labor (%)	7.7	7.6	NS
Labor duration in hrs [‡] (mean $\pm$ SD)	7.0 $\pm$ 2.4	10.0 $\pm$ 6.8	<0.001
(% < 10)	83.3	61.5	NS

* Information based on 90 non-Amish cases.

† Numbers too small to make valid chi-square comparison.

‡ Information available for 24 Amish and 65 non-Amish. Excluded are those individuals with cesarean section or induced labor.

TABLE III. Comparison of Amish and Non-Amish Births for Pregnancy Outcome Characteristics (Chi-square and t-test Analysis)

Pregnancy Outcome Characteristics	Amish (N = 39)	Non-Amish (N = 145)	p Value
Birth weight in g (mean $\pm$ SD)	3,352 $\pm$ 389	3,428 $\pm$ 509	NS
(% $\geq$ 3,400)	36.0	60.0	<0.05
(% < 2,500)	0.0	2.0	NS
Gestational age in wks (mean $\pm$ SD)	39.9 $\pm$ 1.6	39.9 $\pm$ 1.9	NS
(% < 37)	2.6	5.5	NS
1 min Apgar (mean $\pm$ SD)	8.0 $\pm$ 1.1	7.9 $\pm$ 1.5	NS
(% < 7)	7.6	11.7	NS
(% > 8)	33.3	37.9	NS
5 min Apgar (mean $\pm$ SD)	9.1 $\pm$ 0.6	9.0 $\pm$ 1.2	NS
(% < 7)	0.0	1.4	NS
(% > 8)	87.2	91.0	NS

rate in the non-Amish equals the 1987 national average.⁸ Similarly, chi-square analysis showed no statistically significant differences in rates at which oxytocin induction was performed in each group. However, rates of oxytocin induction seemed to demonstrate a trend in the same direction as rates of Cesarean sections.

Overall, there was no indication that being Amish was more conducive for a healthy pregnancy outcome than being non-Amish. This was surprising in view of life style differences and the less technologically mediated life style of the Amish. The non-Amish studied are also rural or small town people who may share many of the same diet practices and physical activities. The Amish and non-Amish prenatal behaviors may be more comparable in terms of risk factors. Amish women keep careful notes on their menstrual cycles to facilitate the Amish midwives' knowledge and record keeping during pregnancies. Prenatal health care and advice during the first trimester may be similar, though the Amish obtain their prenatal health care at this stage from their community midwife, while the non-Amish obtain theirs from a physician.

The reliability of measures such as Apgar scores and gestational age was likely to be strengthened by the fact that all the women studied received prenatal care from a small number of providers, while their newborns were delivered by the same three Tri-County physicians. However, limitations of the study include a small sample size that may have obscured important differences and reduced the ability to generalize the findings. The lack of chart information regarding income status impeded attempts to determine variations in income between the groups, or to control for socioeconomic status in the analysis. As a result, it was not possible to determine the effect that socioeconomic status had on the birth outcomes. Bias may have been introduced because of missing values.

The Old Order Amish are a unique group who continue

a life style reminiscent of rural 19th century Americans. More extensive data from this closed society may provide an opportunity to compare birth outcomes of deliveries by Amish midwives with those by physicians. In addition, studying birthing practices and prenatal advice and care by Amish midwives may provide information helpful to physicians working in areas near Amish communities.

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Football-related spinal cord injuries among high school players—Louisiana, 1989*

During the 1989 high school football season in Louisiana, four high school players sustained cervical spinal cord injuries (SCIs) while playing football. From 1978 through 1988, only three such injuries are known to have occurred in this state (National Center for Catastrophic Sports Injury Research, unpublished data).[†] Louisiana law requires reporting of all SCIs to the Office of Public Health, Louisiana Department of Health and Hospitals.

Three of the injured players were defensive backs, and one was an outside linebacker/tight end. All injuries resulted in quadriplegia; three of the injuries were complete (ie, motor and/or sensory function below the zone of injury was not preserved). The injuries occurred during evening games when the players were tackling or blocking with the head as a point of contact but not in the typical head-down or spearing position. The circumstances suggested that the mechanism of injury was an axial load on a partially-flexed neck and that the vertical force was transmitted down the length of the spine. Previous studies have shown axial loading to be the mechanism most likely to lead to permanent quadriplegia in injured athletes.¹⁻³

The Louisiana Safety and Sports Medicine Advisory Committee, a group formed to address the problem of SCIs among high school football players, is developing an educational program to instruct coaches and trainers on safer methods of tackling. This program may be implemented during the 1990 football season.

Editorial Note: Based on data collected by the National Football Head and Neck Injury Registry for 1971-1975 and compared with data for 1959-1963, the incidence of football-associated cervical SCIs increased from 0.7 per 100,000 participants to 1.6 per 100,000 participants, respectively.³ More than half the injuries identified were attributed to use of the top of the helmet as the initial point of contact. This mechanism of first contact became more common because the modern helmet and face mask, developed in the 1960s and 1970s, offers greater protection in general.³ Because of the increased occurrence of these injuries, in 1976 the National Collegiate Athletic Association (NCAA) and the National Federation of High School Athletic Associations adopted rules prohibiting the deliberate use of the top of the helmet to strike a runner or use of the helmet to butt or ram an opponent.³⁻⁴ The overall decrease in the incidence of quadriplegia in high school football players, from 2.2 per 100,000 participants in 1976 to 0.4 per 100,000 in 1984, was attributed to the

successful implementation of these rules.³

The expected number of football-associated SCIs in Louisiana during 1989 can be estimated in two ways. Based on the 1984 national rate of 0.4 SCIs per 100,000 participants³ and the 1989 population of Louisiana high school football players, only one such injury would be expected during a 14.5-year period. Alternatively, based on the experience in Louisiana from 1978 through 1988, one SCI would be expected during a 3.7-year period. Reasons for the occurrence of the four SCIs during the 1989 high school football season in Louisiana are unknown.

At greatest risk for football-related SCIs are players who tackle by flexing their necks and using the tops of their helmets to strike opponents.¹⁻³ Suggested strategies to prevent football-related cervical SCIs include educating coaches and participants about proper tackling techniques, enforcing existing tackling rules,¹⁻⁶ educating officials about the mechanisms of injury, strengthening the neck with proper conditioning exercises,^{1,6} requiring medical examinations before participation in football and before resumption of participation after injury,^{1,5} and increasing awareness among school administrators and coaches about the proper handling of any player injured during practice or competition.^{1,5,6}

In 1987, the Council of State and Territorial Epidemiologists recommended that traumatic SCIs be designated as reportable.⁷ Strengthening state-based surveillance of SCIs will aid in identifying these catastrophic injuries and assist in the planning, implementation, and evaluation of prevention programs. SCI is a targeted condition in CDC's Disabilities Prevention Program, which supports SCI surveillance and prevention activities in Louisiana.

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The ethics of using scientific data obtained by immoral means

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In March 1988, scientists at the Environmental Protection Agency (EPA) reviewed a study on the effects of phosgene gas, a known carcinogen, on humans. The scientists discovered that data in the draft report cited experiments on "prisoners of war." It turned out that these data had come from Nazi experiments on unwilling victims in concentration camps.¹ Twenty-two EPA scientists wrote a letter to the administrator of the EPA, protesting the use of the Nazi data. The letter touched off a dispute among EPA scientists and others both about the ethics of using the results of the Nazi experiments and about the scientific validity and accuracy of the studies.

Judith Bellin, an EPA toxicologist who initiated the protest letter, called the data "valueless" with regard to their scientific quality since the experiments were flawed on several counts. Furthermore, she stated that, "No matter what the quality of the data is, the Nazi experiments were so heinous that the information should not be used." Other scientists at the EPA argued that such data, if scientifically sound and verifiable, should be used if some good to humans can result. The EPA administrator barred the use of the data. He appointed a committee of senior scientists to formulate policy on the agency's future use of scientific data obtained by immoral means.²

At about the same time, physiologist Robert Pozos, a renowned expert on hypothermia, then working at the University of Minnesota Medical School in Duluth, was preparing material for his hypothermia research. Included were the results of so-called "terminal experiments" conducted by Dr Sigmund Rascher at the Dachau concentration camp. The experiments consisted of throwing prisoners into large vats of freezing water until their body temperatures reached 26° C. Vital signs were checked periodically, and if the prisoners did not die, various re-warming techniques were evaluated. Pozos asked the Center for Biomedical Ethics at the University of Minnesota in Minneapolis for ethical guidelines about using the data. Dr Arthur Caplan, Director of the Center for Biomedical

Ethics at the university, wrote an op-ed piece for a local paper. Pozos was then flooded with calls and letters from Holocaust survivors, journalists, and bioethicists insisting that he not use the data.³

THE UNIVERSITY OF MINNESOTA CONFERENCE

The Center for Biomedical Ethics at the University of Minnesota convened a conference on May 17-19, 1989, to focus on five major themes:

What role did mainstream medicine and science play in the creation of the Nazi state; what did German scientists and physicians think about and do in the name of eugenics and euthanasia; what moral rationales were used to justify the involvement of medicine and science with genocide, euthanasia, and racism; should scientists and physicians make any use of information obtained from barbarous experiments conducted on innocent persons in concentration camps; and what is the appropriate use of metaphors and analogies to the Nazi era in contemporary debates in bioethics?⁴

The conference was videotaped in its entirety by Minnesota Public Television (KTCA), and was broadcast at least twice in Minnesota. Arthur Caplan, the center's director, said that "this meeting is being held because I'm bothered by the fact that [ethical problems relating to] the Holocaust [get] short shrift in the biomedical ethics texts."³ Caplan and others at the conference argued that the racist underpinnings of Nazi ideology were firmly rooted in the racial hygiene theories prominent in German biology during the 1920s and early 1930s—well before Hitler came to power. Nazism was not a philosophy espoused on the fringes of German medicine and science. Rather, it had roots deep in the mainstream of German biology, medicine, and public health.

"The whole discipline of biomedical ethics rises from the ashes of the Holocaust," said Caplan. He listed many of the infamous experiments that the Nazis conducted: Women at Ravensbruck were mutilated to test the effectiveness of drugs against gunshot wounds and other simulated battlefield injuries. High altitude decompression experiments using Jews and other prisoners resulted in at least 80 deaths among the 200 subjects used. Gypsy and Jewish twins were Dr Joseph Mengele's special interests.

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In one of his infamous experiments, he used injections to try to change eye color from brown to blue to create perfect Aryans. "We have to keep in mind the suffering of these people," said Caplan, "these are the ghosts we have to bear."

The acts of medical experimentation and torture chronicled at the Nuremberg trials had a chilling effect on the world at large and the medical profession in particular. Lifton⁵ recounts in great detail the involvement of German physicians in the torture and killing of thousands of innocent human beings. The Nazis established a program of sterilization and "euthanasia" under which German physicians murdered countless children and adults. These individuals were considered unworthy of life, because they were physically or mentally ill, or socially undesirable (eg, Jews). The Nazi program climaxed at Auschwitz, where doctors chose those who were to die, supervised the killings in the gas chambers, and determined when the victims were dead. Doctors ordered, supervised, and at times carried out the killing of debilitated patients on the medical blocks. At the same time, they kept up a pretense of medical legitimacy by signing false death certificates listing spurious illnesses. Doctors helped determine how many people should be kept alive to fill the slave-labor requirements of the IG Farben enterprise at Auschwitz and gave advice on how to dispose of the enormous numbers of bodies produced by the gas chambers.

At Auschwitz, Jews, Gypsies, and others were sterilized by injection, radiation, or surgery, injected with vaccines made from dental infections, subjected to massive bleedings for blood-group experiments, brainwashed with chemicals, infected with typhus, and exposed to toxic substances. Vivisections were performed and human flesh was used for culture media as well as the making of lampshades and tobacco pouches.

In sum, doctors supervised the entire killing process at Auschwitz from beginning to end. How were physicians, sworn by oath and conviction to ease suffering, transformed from healers to systematic killers? At the Minneapolis conference, Caplan reviewed the moral rationales advanced by Nazi physicians at the Nuremberg trials. He noted that the German physicians who administered the euthanasia program, supervised mass genocide, and conducted brutal experiments on Jews and other groups in concentration camps grounded their actions on utilitarian principles. They maintained that the state was justified in sacrificing the minority to advance the interests of the majority—only those "doomed to die" anyway were selected for research involving lethal experiments.

Dr Jay Katz, professor of law at Yale University, reviewed the atrocities perpetrated by Nazi scientists in the name of *scientific* research. He concluded that "the ability to undertake murderous science was grounded in five norms: obedience to authority; a commitment to racial superiority; a concern for the security and well-being of the state in time of war; a belief in the importance of scientific progress; and an ethos of (pseudo-) professionalism that held that patients' interests were best served by trusting their doctors."⁴ When the controversy broke over the EPA study, Katz first thought that Nazi data should be used, but after greater consideration, he concluded the opposite.

The most emotional part of the conference concerned

the ethics of using data obtained from experiments on victims from concentration camps. Dr Robert Pozos (see above) argued that Nazi research on hypothermia, while cruel and often fatal, was scientifically sound and the only source of information about exposure to extremely cold temperatures; it should therefore be used. Pozos' position was heatedly and passionately attacked by two survivors of medical experiments at Auschwitz, Eva Kor and Susan Seiler Vigorito. Dr Robert Berger, Professor of Surgery at Harvard University School of Medicine and himself a survivor of the camps, questioned the scientific validity of the Nazi experiments and the claim that they are the sole source of information about exposure to cold temperatures.

No consensus emerged from the conference about the ethics of using Nazi findings. It did become clear, however, that "Nazi data and the claims of Nazi science in areas such as genetics, physiology, pathology, anthropology, and psychiatry have in the past been studied, cited, and absorbed into mainstream science with little comment."⁴ The Dachau hypothermia experiments are often cited in the medical literature without comment⁶⁻⁷ although an occasional article calls them "sordid investigations."⁸

THE BOSTON UNIVERSITY SCHOOL OF MEDICINE CONFERENCE

On December 4-5, 1989, a conference was presented by the Law, Medicine and Ethics Program of the Boston University Schools of Medicine and Public Health in conjunction with the B'nai B'rith Hillel Foundation at Boston University. Entitled "The Nazi Doctors and the Nuremberg Code: Relevance for Modern Medical Research," the conference reviewed the inhumane Nazi experiments which left thousands of prisoners dead and many others physically and emotionally scarred.

The speakers differed about the ethical principles of the use of data from Nazi medical experiments already known to be in the mainstream in "at least 45 articles, mainly on hypothermia which have been published in court documents and German medical journals, and . . . cited in mainly refereed journals."⁹ Some researchers wanted to use this data to "salvage some good from the ashes," while at the same time indicating the monstrous manner in which the results were obtained. Others argued that there are no circumstances under which the results should be used since they are untrustworthy and cannot be applied to the general population. They argued further that even if the results were sound, they should not be dignified with scientific respectability because of the heinous manner in which they were obtained.

Conference codirector George Annas, Professor of Health Law at Boston University School of Medicine, said that the issues surrounding the Nazi data are too emotional to be fully resolved, but that "more general issues involving use of unethical research results still apply to the care of dying patients, euthanasia, trials of new drugs for acquired immunodeficiency syndrome, fetal tissue transplantation and genetic engineering."⁹ In this regard, Dr Marcia Angell, executive editor of the *New England Journal of Medicine*, stated that, "Unethical research is undoubtedly still being conducted but results of such studies are not accepted for publication by the

Journal. The first hurdle a manuscript must survive is the ethical one, and until that is cleared, the article's scientific merit is irrelevant" (ie, studies are not ethical just because they are useful).¹⁰

THE KENT STATE UNIVERSITY CONFERENCE

On March 20–21, 1990, the Ninth Annual Holocaust Conference at Kent State University in Ohio was devoted to "Holocaust and Biomedical Ethics: The Contemporary Use of Nazi Data." Similar presentations to those made at the University of Minnesota and the Boston University Conferences described above were delivered. The arguments and ethical concerns expressed were the same at all three conferences.

BRAINS AND SKELETONS OF NAZI VICTIMS AT GERMAN UNIVERSITIES

In 1988, a psychiatrist in Dusseldorf, West Germany, reported that two of the brains of schizophrenics that he had studied and previously published data about¹¹ came from Holocaust victims. He said that "in future studies, therefore, we will not evaluate the brains of these two patients who died during the darkest chapter in German psychiatry."¹² In an accompanying comment, Gershon and Hoehe¹³ describe the known facts concerning the deaths of the two patients and concluded that they were probably murdered as psychiatric patients in the Nazi "euthanasia" program.

In early 1989, West Germany's ARD television network broadcast claimed that tissue samples and skeletons from the corpses of victims of Nazi-era executions were still being used at West German medical schools.¹⁴ The institutions involved included the Universities of Tübingen, Heidelberg, Cologne, and the Max Planck Institute of Brain Research. Between 1933 and 1945 the University of Tübingen received 1,077 bodies from an execution site in Stuttgart. The University of Heidelberg obtained cadavers from a prison and from the mental hospital at Hadamar, which was notorious for its involvement in the "euthanasia" program. Investigation of the origin of the Tübingen specimens followed an inquiry by medical students who demanded a deeper evaluation of the Nazi legacy in West German medicine and raised serious ethical questions about teaching exhibits.¹⁵ At the University of Cologne, the use of brain sections from the Nazi period was discontinued after a protest by a faculty member and students, though specimens from other organs reportedly remained in use.

The Israeli Religion Minister demanded that West German Chancellor Helmut Kohl immediately deliver all body parts from Nazi victims for proper burial. Kohl called on the universities to stop using any such remains and added that these practices "should have ended 40 years ago."¹⁴ The University of Tübingen appointed a commission to investigate the matter. The University of Heidelberg tried to decide how best to dispose of the samples in its anatomical collections. The Max Planck Institute announced plans to give a respectful burial to the tissue samples from the brains of Nazi euthanasia victims that remained in its collections.¹⁶

According to one writer, the discovery of the anatomical specimens should force medicine to face the facts of

the Nazi era by creating a symbol that sensitizes the profession to its potential for evil. The proposed burial of these remains, and subsequent anniversary commemorations, could provide such a symbol.¹⁵

OTHER UNETHICAL EXPERIMENTS

Immoral medical experimentation is not limited to the heinous acts of the Nazis. In a now classic 1966 article entitled "Ethics and Clinical Research,"¹⁷ Beecher reviewed 50 studies of unethical or questionably unethical procedures. These contained references to 186 additional probable instances. Furthermore, he cited a British colleague who had collected more than 500 papers based on unethical experimentation. For example, Beecher reviewed a study in which 109 servicemen with acute rheumatic fever were given a placebo while others received appropriate penicillin therapy. In a study of 408 charity patients with typhoid fever, 251 were treated with chloramphenicol and 157 were not treated. The death rate was three times as high for the untreated patients (22.9% vs 7.97%). The efficacies of penicillin and chloramphenicol were already well established. In other studies, "mental defectives" and "juvenile delinquents" were given an experimental drug to study its potential hepatotoxicity, and hepatitis was artificially induced in retarded children.

Beecher cites other unethical studies, such as the injection of live cancer cells into 22 human subjects who were told only that they would be receiving "some cells"—the word cancer was entirely omitted. In an effort to determine whether ureteral reflux occurs in normal bladders, 26 neonates were subjected to vesicourethrography, with radiographs taken during bladder filling and voiding.

Beecher concluded his article by saying that "an experiment is ethical or not at its inception; it does not become ethical *post hoc*—ends do not justify means."¹⁷

In 1973, Capron reviewed experiments performed on prisoners in American penitentiaries. The studies included repeated bilateral testicular biopsies with injection of radioactive thymidine to study the rate of spermatogenesis; drug testing; plasmapheresis programs resulting in infection, illness, and at least six deaths; use of a muscle paralyzing drug on "extreme acting-out criminal offenders"; use of prisoners as organ donors; artificial creation of typhoid fever and other infections including *Staphylococcus aureus*, *Candida albicans*, and *Pseudomonas*; and artificial induction of scurvy. Capron called for a moratorium on medical research in prisons.

Perhaps the most infamous immoral research performed in this country was the Tuskegee, Alabama, syphilis experiment which began in 1932, before the Nazis' ascent to power, and continued until 1972, after media disclosure gave rise to a public outcry. Four hundred black men suffering from syphilis were left untreated so that the natural course of the disease could be studied.

PUBLICATION OF UNETHICAL RESEARCH

During the same year that Beecher concluded that "it is debatable whether data obtained unethically should be published even with stern editorial comment,"¹⁸ Curran reported on a survey of editorial policies and practices. The survey, conducted by the Boston University Law Medicine Institute, found that "most medical-journal edi-

tors did not see as one of their responsibilities the checking or monitoring of papers submitted to insure that the researchers had followed accepted ethical practices to protect the subject's rights in experimental situations."¹⁹ Nevertheless, for years, repeated suggestions have been made to suppress publication of unethical research.²⁰

In a provocative article entitled "Ethics and Editors," Brackbill and Hellegers²¹ reported the results of a survey of editors of 138 "core medical journals," inquiring about the extent to which ethics are considered in reviewing manuscripts submitted for publication. Fifty-nine percent of editors said they do not instruct reviewing editors to judge manuscripts on the basis of ethics. Seventy-three percent of editors do not require authors to submit institutional review board (IRB) approval along with their manuscripts. More than 72% of editors agreed with the proposition that "the most effective way to eliminate ethical violations in research is for editors to refuse to publish articles based on research in which there are clear ethical violations." Eighty-nine percent of editors contemplated no changes in editorial policy with respect to any of the points cited above.

The authors of this study concluded that most editors believe that the observance of ethical standards in research is a precondition for publication, and that editorial responsibilities include ethical responsibilities. On the other hand, most editors have no policy with respect to ethical review at the editorial level or institutional level. In a commentary following the Brackbill and Hellegers report, the editor of *The New England Journal of Medicine* opined that "careful editorial review is more important in maintaining ethical standards than is any requirement that papers contain statements about informed consent or IRB review."²² The editor of the *American Journal of Public Health* cited instances of double-blind trials in a primitive community where written informed consent in the American sense was out of the question, and instances in the United States in which deliberate deception occurred in research oriented toward consumer protection. In both instances, the articles were published together with editorial disclaimers.²³ The editor of *Public Opinion Quarterly* said, "I do not believe it is the function of an editor to act as an ethical gatekeeper."²⁴

THE USE OF NAZI RESEARCH DATA

The tremendous current interest in the morality or immorality of using the Nazi research data was precipitated by the EPA phosgene study, the Pozos hypothermia research at the University of Minnesota, and the recent discovery that brains and skeletons of Nazi victims are being used to teach anatomy at German universities. Should one simply use the Nazi research data? Should one reject it on moral grounds and only cite other legitimate research? Should one use the data but cite it only with an explicit condemnation of Nazi methods?

In 1984, Moe²⁵ discussed the question of what to do about research, now labeled unethical, that has already been published. She maintains that use of data from Nazi research is justifiable under certain conditions: The data must be reliable, unavailable from any other source, capable of contribution to the greater good, and publication must be accompanied by a clear condemnation of the

means by which the data were collected. Sheldon and Whitely²⁶ posit that the fundamental obligation of medicine is to protect and to preserve life. Therefore, if the data can contribute to the saving of lives, it should be used. On the other hand, Folker and Hafner²⁷ state that if a scientist cavalierly gives inhumanely extorted data a place in his work, public confidence is rightly shaken. They recommend that the Nazi data be rejected. Gaylin²⁸ opines that to use this data is to give it, beyond credence, honor. He further states that

The Nazi medical experiments were but threads in the tapestry of evil that was the Holocaust, but no thread must be dignified by its utility. We must not add our numbers to the multitudes of onlookers who slept peacefully through the nights of anguished cries while dreaming their sweet dreams of a better tomorrow.

In an extensive discussion of the ethics of using medical data from Nazi experiments, Cohen²⁹ addresses the scientific validity of the experiments, the medical competence of the experimenters, the social utility in using the experimental data, case studies of proposed uses of the Nazi scientific data, and the policy considerations involved when scientists use immorally obtained data. He concludes that if the value of Nazi data is of potentially overwhelming benefit to humanity, the morally appropriate policy should be to utilize the data while explicitly condemning the atrocities. Britain's Chief Rabbi Lord Immanuel Jakobovits³⁰ expresses serious doubt as to "whether the diabolical cruelties inflicted by Nazi physicians ostensibly in the name of medical progress did, in fact, yield any significant results of direct benefit to humanity." Even if the most evil mass perversity in human history did produce valid data, the innocent victims of such degradation would be the last to support the use of such data. They would have wished, concludes Jakobovits, that the sacrifice of their lives would contribute to an era when such inhumanities would be unthinkable. Various arguments in favor of using the Nazi research data, such as the utility of the data, consequentialist and retributive arguments, the argument from ceremony, and "the best of both worlds," are espoused by Martin.³¹ All these arguments are rebutted and rejected by Schafer.³²

UNETHICAL RESEARCH TODAY

The discussion about the possible benefits to mankind from Nazi research data should finally come to an end with the recent demonstration by Berger³³ that the Dachau hypothermia experiments were severely flawed and yielded no scientifically valid data. The project was conducted without an orderly experimental protocol, the methods were inadequate, and the execution was erratic. Berger also shows that the Dachau report is riddled with inconsistencies, data falsification, and fabrication, and that many conclusions are not supported by the facts presented. Furthermore, Berger reports that the director of the project showed a consistent pattern of dishonesty and deception in his professional as well as his personal life, thereby stripping the study of the last vestige of credibility. Berger concludes that "the Dachau hypothermia study has all the ingredients of a scientific fraud, and rejection of the data on purely scientific grounds is inevita-

ble. They cannot advance science or save human lives.”³³

In view of the scientific worthlessness of these Nazi experiments, the debate about whether to use Nazi data is now moot. There are no useful data. However, unethical research was conducted long after the Nuremberg trials, and some even continues today. Examples described by Beecher, including the Willowbrook hepatitis study and the Tuskegee, Alabama, syphilis study, have already been cited.¹⁷ Some writers express revulsion at the psychosurgery research that took place in this country in the 1930s, 1940s, and 1950s. On the other hand, can we hold researchers in 1950 responsible for the moral code of 1990? Can we judge experiments in the first half of this century by present day moral standards?

According to Angell,³⁴ unethical research of today reflects thoughtlessness more than callousness. She cites as examples the glossing over the requirement of informed consent to yield faster and more useful results, and the use of a placebo group where there is reason to believe the treated group will fare better. She decries the fact that “journal editors and peer reviewers sometimes encourage these practices by emphasizing scientific over ethical rigor.” *The New England Journal of Medicine* has taken the position that it will not publish reports of unethical research, regardless of their scientific merit, because “knowledge, although important, may be less important to a decent society than the way it is obtained.”³⁴

CONCLUSIONS

The debate about the use of Nazi research data should now end with the clear demonstration that the most widely cited of such data, the Dachau hypothermia experiments, are scientifically worthless. The debate continues about the use and/or publication of unethical research in the post-Nazi era, including the present time.

The Committee on Bioethical Issues of the Medical Society of the State of New York condemns unethical scientific experiments of any type. The immorality of the cruel World War II experiments has to be considered in a special category, and data stemming from them, even if they were scientifically valid, should not be used. No research based on the fundamental premise that any group of people is “subhuman” should be given acceptance in a civilized society.

Other scientific data obtained in the past by immoral means that might be useful in saving human lives may not be irredeemably tainted. It may be morally justifiable to use such data under certain limited circumstances to save lives provided that the immorality of the experiments is condemned with an appropriate disclaimer.

It seems important to make the distinction between experiments that should have been seen as inhumane and outrageous at the time they were done and experiments that were done by well-meaning and indeed ethical individuals according to the accepted standards of their time. A lot of research in the 1940s and 1950s, done on prisoners or on soldiers, would be unethical if done now. However, at the time, the prisoners had the chance to serve humanity and the soldiers were helping to learn how to win wars. If the studies were on healthy persons, the subjects were volunteers; if on sick soldiers, the studies were designed to try to help them and/or get them back to battle most

quickly. For the most part, the prisoners and soldiers had a reasonable understanding of the risks involved and were willing to undergo those risks. The studies were therefore ethical if the design was valid and the results likely to be helpful to mankind. Experts would probably condemn similar experiments if proposed today, because society’s view of what is and is not ethical in research has changed considerably in the past three or four decades. Certainly, there were major advances in medicine in the post-World War II era that would not have been made without experiments we would now consider unethical.

Current and/or future investigators should be barred from using immoral research methods. Ethically unacceptable studies and reports should not be accepted for publication by journal editors or peer reviewers, and, if already published, should not be rewarded by citation in respected medical journals. “To publish such data in a scientific journal is to legitimize it.”²⁸

Science and medicine must assure that research is moral, ethical, proper, and humane. Because of the many well-documented abuses and the imperative to prevent their recurrence, the concepts and foundation of proper research have developed in recent generations. Much impetus came by law, regulation, and guidelines. However, the critical control is maintained by the researchers themselves based on their own innate code of ethics, to which is added learning, both formal—teaching of proper research and its conduct—and informal—teaching by precept and example by mentors and peers.

Significant contributions in this regard are made by institutional review boards (for human studies) and by institutional animal care and use committees. With their work appreciated and supported, these committees are powerful forces not only as overseers but also as teaching mechanisms.

Neither thoughtlessness, nor callousness, nor glossing over ethical or scientific requirements is excusable. Researchers must learn that research must have a rational basis and adhere to principles of moral and ethical behavior.

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FROM THE LIBRARY

NAZI PHYSICIANS

As this is being written at least 23 doctors of medicine and numerous German scientists, medical administrators, and others are being brought to trial for "atrocities" against prisoners, the indictments being under four counts: conspiracy, war crimes, crimes against humanity, and membership in the criminal organization of the Elite Guard which practiced a macabre science of killing.¹

At the request of the Federal government, the Board of Trustees of the American Medical Association delegated Dr. A. C. Ivy, vice-president of the University of Illinois, "To represent the Association in an investigation of these acts of inhumanity..."²

The trials will develop the testimony and show the degree of participation and guilt of these physicians in such acts of inhumanity. To us, the abandonment of all professional restraint, departure from rigid codes of ethical conduct based on the welfare of the individual patient seems inconceivable. The foundation of the confidence in any physician by his patient is based upon the belief that the doctor, with all available knowledge and means, will fight to the last ditch to alleviate suffering and to cure if possible. This is the doctor-patient relationship, the sine qua non of the art of medicine. It permits of no compromise, no discrimination, no relaxation of vigilance.

The sorry and degrading thing to which some Nazi doctors allegedly descended merely serves to illustrate, in our opinion, the dangerous impact of political ideology on professional standards. In this instance it was the lunatic doctrines of Hitler's debased philosophy. But what occurred as a result, exemplified by these tragic instances, should be thoughtfully considered by those who would promote "state medicine."

Control over medical education, medical practice, and medical science by the state can, in extreme cases such as these, produce extreme moral degradation. But these instances are merely the outstanding examples. What of civil practice under statism?

In an era of rapid scientific discovery not only in medicine, but also in theoretic mathematics, physics, chemistry, and allied fields the capture of the medical profession by the system of state socialism initiated by Bismarck in Germany did not hinder but actually assisted the growth and progress of medical science by throwing behind the universities the resources of the state. One remembers the initial progress made with admiration.

But if the financial resources of the state were of benefit initially to medical science, these benefits could not be divorced from the political system which produced them. Medicine was thus integrated into the system of state socialism with the result that it became dependent utterly upon the system. The result we have seen.

As the state deteriorated to national socialism under inhuman and perverted leadership, medicine and medical men deteriorated likewise. It is well to remember from this object lesson that what the state can do *for* you is often not so important as what the state can do *to* you. It is something to think about.

¹ New York Times, Dec. 10, 1946.

² J.A.M.A. 132: 714 (Nov. 23) 1946.

(*NY State J Med* 1947; 47: 363)

Pneumonia and intracranial lesions following therapeutic remission of acute lymphoblastic leukemia

CASE PRESENTATION

Patrick N. Dwyer, MD (Attending Physician, Hematology/Oncology): A 65-year-old woman was admitted to Mary Imogene Bassett Hospital with a white blood cell (WBC) count of 36,300/ μ L. The patient's history included insulin dependent diabetes mellitus, obesity, hypertension, probably angina, cholelithiasis, osteoarthritis, and gingivitis. Her surgical history included a total abdominal hysterectomy and salpingo-oophorectomy, with a subsequent ventral hernia repair and persistent fistula drainage associated with a graft. She had smoked cigarettes in the remote past.

In addition to the total WBC count of 36,300/ μ L, a differential WBC count disclosed 1% polymorphonuclear leukocytes. There were a number of immature clefted and lobulated lymphoid cells reminiscent of lymphosarcoma cell leukemia. The platelet count was 21,000/ μ L; the bone marrow aspirate was a "dry tap"; marrow biopsy showed diffuse infiltration with immature lymphoid cells compatible with non-Hodgkin's lymphoma. Immunophenotyping of these cells was positive for SIg, cALLA, and TdT, supporting the diagnosis of acute lymphocytic leukemia, with an aberrant pre-B cell phenotype as indicated by positive surface immunoglobulin, Ia and B4.

Four days after admission, chemotherapy was started with cyclophosphamide, doxorubicin, vincristine, and prednisone (80 mg/day). The following day, the patient experienced "neutropenic fever" with a urinary tract infection, and blood cultures were positive for *Escherichia coli*. She was treated with ticarcillin, gentamicin, clindamycin, and nystatin, following which her temperature returned to normal.

Two weeks after admission, stomatitis developed, proven by culture to be due to herpes simplex type I (HSV-1), and treatment with acyclovir was begun. On the 19th hospital day, following clearing of blast forms on the peripheral blood smear, cytologic examination of the cerebrospinal fluid revealed no malignant cells. Three intrathecal doses of methotrexate were subsequently administered.

By the middle of the fourth hospital week, the patient's neutrophil count had transiently recovered with a total count just below 1,000/ μ L. The following day (day 22 of therapy), she again received chemotherapy. Her hospital course had, in addition, been complicated by hyperglycemia, thrombocytopenia responsive to platelet transfu-

sions, stool guaiac tests positive for blood, and, probably, gentamicin-associated ototoxicity. She was discharged with plans for readmission in the event of neutropenic fever.

Six days following discharge, shaking chills, confusion, and lightheadedness developed. Physical examination on readmission to the hospital disclosed the following: in the supine position, the patient's blood pressure was 135/60 mm Hg, and the pulse was 138/min; in the sitting position, her blood pressure was 86/52 mm Hg, and her pulse was 140/min; respiratory rate, 28/min; and temperature, 39.2°C. The patient was markedly confused; a flame-shaped hemorrhage was present in the left ocular fundus. The WBC was 44/ μ L; hematocrit, 36%; platelet count, 27,000/ μ L; and blood glucose, 179 mg/dL. Blood cultures were positive for two biotypes of *Escherichia coli*, *Klebsiella* sp, and enterococcus. With a diagnosis of sepsis associated with profound neutropenia, treatment with ceftriaxone and aztreonam was begun and was followed by prompt return of temperature to normal and clearing of mental confusion, but with residual expressive aphasia. A computed tomographic (CT) scan of the head revealed a left parietotemporal hemorrhage.

By the fourth hospital day, the total polymorphonuclear WBC count was 1,000/ μ L and remained at normal levels throughout the patient's hospital stay; vancomycin was added to her antibiotic treatment, and her dose of prednisone was reduced to 20 mg/day, because of presumed central nervous system infection.

One week after admission, a venous duplex scan disclosed a probable right calf venous thrombus; anticoagulant therapy was not initiated because of the recent intracranial hemorrhage. On the ninth hospital day, prednisone was discontinued, but the patient began to complain of left facial dysesthesia, right finger paresthesia, and right leg weakness. The following day, a CT scan of the head revealed a resolving intracranial hemorrhage, but with a persisting mass effect.

On the 12th hospital day, the patient was again confused, with persistence of the right leg weakness and facial dysesthesia; prednisone, 60 mg/day, was ordered in an attempt to decrease brain edema. Two days later, a repeat CT scan showed some residual intracranial hemorrhage and brain edema. At this time the patient complained of right lower quadrant abdominal pain; her alkaline phosphatase was 476 U/L. A CT scan of the abdomen disclosed two hypodense lesions in the liver, and prednisone was tapered to 50 mg/day.

The patient's lethargy and confusion persisted; on the 21st hospital day, a chest film showed infiltrations in the

Based on a clinicopathologic conference held at Mary Imogene Bassett Hospital, Cooperstown, NY, on March 6, 1990.

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right upper lobe and at the lung bases; fundoscopic examination revealed no evidence of infectious emboli. On the following day, prednisone was reduced to 30 mg/day; cotrimoxazole was given together with an amphotericin test dose.

By the 23rd hospital day, the right upper lobe infiltrate was increasing in size on the chest film. Bronchoscopy with bronchoalveolar lavage and biopsy demonstrated *Acinetobacter species* on culture sensitive to ceftriaxone, but was negative for fungus, *Pneumocystis carinii*, and acid-fast bacteria. The following day, a CT scan of the head revealed a ring-enhancing lesion, most probably representing an abscess. A CT scan of the abdomen revealed no change in the hepatic lesions. The serum alkaline phosphatase level was 757 U/L. Treatment with amphotericin for possible fungal infection and metronidazole for possible occult anaerobic infection was begun; the prednisone dosage was reduced to 25 mg/day.

On the 28th hospital day, the patient experienced a seizure, with evidence of both hypoglycemia and hypomagnesemia. Treatment with amphotericin was discontinued. A repeat CT scan of the head revealed several ring-enhancing lesions, suggesting progression of the intracranial infection. Treatment with penicillin, 3 million units every four hours, was begun. Bone marrow biopsy indicated a hypocellular marrow in remission from leukemia.

On the 34th hospital day, a CT scan of the head revealed multiple ring-enhancing lesions in the brain; because of fluctuating central nervous system symptoms, a brain biopsy was performed; this disclosed infarcted brain tissue and was initially negative for infecting organisms. The serum alkaline phosphatase level was 1,211 U/L. Six days later, closer review of the brain biopsy identified rare mycelial elements, and treatment with amphotericin B was again initiated. The patient's condition slowly deteriorated, however, and she died on the 39th hospital day.

This patient had acute leukemia with prolonged neutropenia; she received steroid therapy for a period of 51 days in a clinical setting of diabetes and sepsis. She also received broad-spectrum antibiotics. Presumed invasive fungal infection developed and was characterized by progressive central nervous system lesions, which were positive for fungi on brain biopsy. Other developments included abdominal discomfort, pulmonary infiltrates, hepatic defects, and elevation of the serum alkaline phosphatase level.

After reviewing the patient's radiographs, we will discuss the nature of infection in acute leukemia, especially the risk factors for and the incidence of invasive fungal disease in that setting. We will discuss the difficult diagnostic problems associated with fungal diseases, the organisms involved in fungal infection in acute leukemia, some of the related clinical syndromes, the commonly applied therapy, and the prognosis associated with complications caused by the intensive treatment required to control the primary malignancy in these patients.

The radiographs will be reviewed by Dr Chanamolu.

RADIOLOGIC PRESENTATION

Vittal B. Chanamolu, MD (Attending Radiologist): A noncontrast CT scan of the head on the third hospital day showed an area of increased attenuation in the left tempo-

roparietal region, most likely representing a hemorrhage; it was surrounded by lower attenuation edema. The hemorrhage cleared on a subsequent CT scan, but the edema in the left temporoparietal area tended to persist.

The CT examination of the abdomen on the second hospital day revealed no intrahepatic defects, but a repeat CT scan on the 17th hospital day showed two low attenuation lesions in the right lobe of the liver.

The chest film on the 21st hospital day showed parenchymal alveolar infiltrations in the right upper lobe of the lung and at the left base, findings compatible with pneumonia.

On the 24th hospital day, the contrast-enhanced CT scan of the head showed a lesion in the left temporoparietal area, with ring enhancement and surrounding low-density edema (Fig 1).

In a patient with acute lymphocytic leukemia and evidently disseminated infection, the lesions in the brain and liver represent abscesses; the patient also had pneumonia. Most likely these findings resulted from invasive fungal disease.

Dr Dwyer: Several elements are responsible for the uniform occurrence of infections in patients treated for acute leukemia. Firstly, granulocytopenia is the most significant factor, with a direct relationship between the duration and depth of granulocyte nadir and the incidence of infections.

Damage to anatomic barriers as a consequence of the chemotherapy for the leukemia can result in gastrointestinal mucosal damage, thus allowing invasion by microorganisms. Placement of intravascular catheters, urinary catheters, and other invasive medical procedures also may allow ingress of microorganisms.

Lastly, the endogenous microbial flora may be altered in patients with acute leukemia who are hospitalized and treated for the disease. Such patients can either lose their resistance to the organisms that normally colonize the skin and internal passageways of the body, or conversely, the patients may acquire new resistant organisms in the microenvironment, which then become responsible for in-

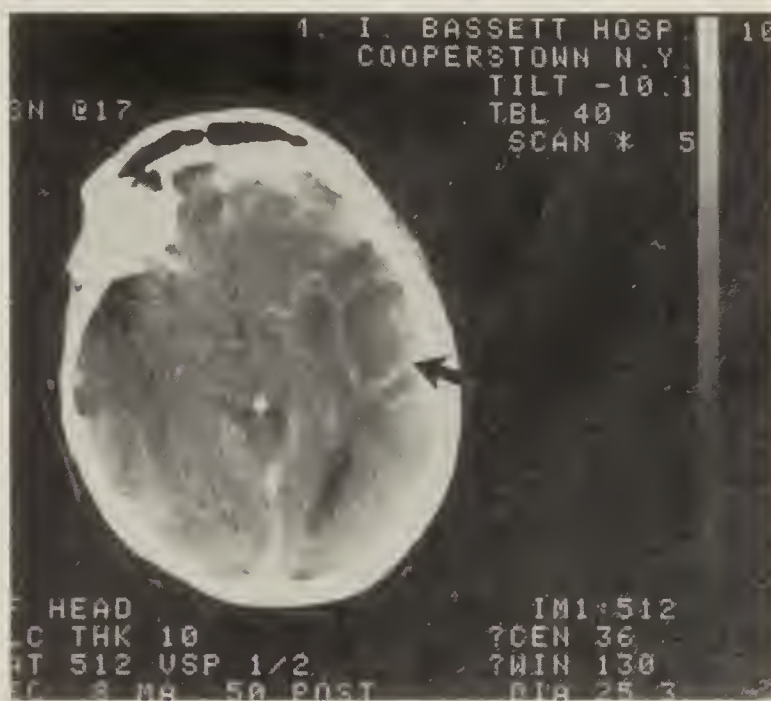


FIGURE 1. Computed tomographic (CT) scan of head, showing lesion (at arrow) in left temporoparietal area, with ring enhancement and surrounding low-density edema.

fections.

Susceptibility to fungal infection, however, involves a number of dominant risk factors. The most important is duration of neutropenia, which, with the more aggressive chemotherapeutic regimens, is becoming a more common factor in hospitalized patients. The duration of the hospital stay, early onset of neutropenia, development of neutropenic fever, the use of broad-spectrum antibiotics (especially of the more potent agents), corticosteroid therapy, diabetes, invasive medical procedures, and catheters all have a strong relationship to the development of fungal infection in acute leukemia. All were important in this patient's case.

In addition, parenteral nutrition, poor control of the underlying malignancy, multiple positive surveillance cultures, and, especially for *Aspergillus*, hospital construction activity are all additional risk factors for the development of fungal infection in acute leukemia.

The incidence of fungal infection in patients treated for acute leukemia, as reported in the medical literature, varies from 10% to 40%. A truly accurate statistic is difficult to ascertain, because most fungal infections are only definitively diagnosed at autopsy. In a review of our autopsy series, which spans a ten-year experience at this hospital, we identified 11 patients with acute leukemia who underwent complete autopsies. Seven of those patients had been in the hospital for more than five days, and of those, six died with invasive fungal disease. One patient had disseminated mucormycosis, another had aspergillus pneumonia, a third developed aspergillus pneumonia with concomitant ulcerative gastrointestinal candidiasis, a fourth had splenic candidiasis, another had candidal pneumonitis, and the sixth patient had candidal sepsis and ulcerative gastrointestinal candidiasis.

The diagnosis of fungal infection in acute leukemia is difficult. There are three ways to make this diagnosis: as a presumed diagnosis, for which empiric therapy is administered; by biopsies, frequently of deep organs; or at the time of autopsy. It is important to recognize that mucosal colonization by itself does not necessarily imply invasive fungal disease, as such colonization is common during chemotherapy for leukemia. Consequently, surveillance cultures for fungi are usually not very helpful. Identification of *Aspergillus* from nasal swabs is useful in suggesting aspergillosis, and *Candida* in particular can be found regularly in the normal gastrointestinal tract; however, serodiagnosis of fungal disease in these instances, using antibodies or antigens, is remarkably unreliable. Positive blood cultures are infrequent with invasive fungal disease and almost nonexistent with *Aspergillus*.

As many as 85% of patients with acute leukemia who develop invasive fungal disease will not have an antemortem diagnosis of that infection. When considering the possibility of invasive fungal disease in acute leukemia, a high index of suspicion should be maintained. This is especially important for patients who have prolonged neutropenic fever, particularly in the presence of a poor overall clinical response to broad spectrum antibiotics, and when no specific infecting organisms have been identified. In addition, a satisfactory clinical response to empiric antifungal therapy supports the diagnosis of invasive fungal disease.

In this patient, the bronchoscopy with bronchoalveolar

lavage and biopsies failed to reveal any fungal organisms. The series reported by Saito et al¹ included 22 leukemic patients who underwent bronchoalveolar lavage within three weeks prior to autopsy. All were neutropenic, had pulmonary infiltrates on chest films, and were under treatment with broad spectrum antibiotics; 15 of these 22 patients were being treated with amphotericin B. In three of the four patients found at autopsy to have candidal pneumonia, the bronchoalveolar lavage had demonstrated marked numbers of *Candida* organisms; however, none of the nine patients shown at autopsy to have aspergillus pneumonia had had supportive findings on their bronchoalveolar lavage. In this series of 22 patients, bronchoalveolar lavage did not lead to any change in the therapeutic regimen; there were no complications of the procedure.

This series by Saito et al¹ is reminiscent of the general experience with open lung biopsy in the management of febrile neutropenic, leukemic patients. Diagnostic accuracy is improved in identifying aspergillosis, but the procedure has little impact on patient therapy and of course carries a significant degree of morbidity.

The organisms involved in invasive fungal disease in acute leukemia are many; however, in the series of Gold,² from the Sloan-Kettering Institute, 68% of invasive fungal disease was caused by *Candida*, 27% by *Aspergillus*, and 5% by *Mucor*. Other fungal species, such as *Trichosporon*, *Fusarium*, *Pseudoallescheria*, and others are rare, but are being increasingly identified in invasive fungal disease.

The three most common organisms display a variety of clinical syndromes. Candidiasis is the most frequent invasive fungal infection in acute leukemia with neutropenia. *Candida* colonizes the mucosal surfaces in the presence of defects in CD-4 lymphocyte function. However, neutropenia and functional defects in neutrophilic leukocytes are the two conditions most frequently responsible for invasive disease. Generally, *Candida* effects its entry into the body through the gastrointestinal tract and occasionally through a catheter or a genitourinary source. Oral pharyngeal colonization can be demonstrated in 88% of patients with neutropenic candidiasis, and colonization of the urine in 71%.

These patients usually present with fever that does not abate with antibiotic therapy. At autopsy, such patients have widely disseminated disease; 92% have involvement of the liver, 83% invasion of the lung, and 75% splenic involvement, as well as significant infections of the kidney, heart, and brain. Clinically recognizable syndromes include macronodular skin lesions; the syndrome of muscle pain and tenderness, known as candida myositis; and the development of retinal exudates or endophthalmitis. Frequently, patients will have pulmonary infiltrates, hepatomegaly, and the late development of septicemia, with a mortality of between 50% and 80%.

The therapy for neutropenic candidiasis is amphotericin B. The clinical outcome is strongly related to the early identification of this illness and the administration of appropriate doses of amphotericin B. In the series of patients reported by Degregorio et al,³ two thirds survived among those patients whose fungal disease was diagnosed antemortem and who received a dose equal to or greater than

0.3 mg/kg/day. There were no survivors among those patients who received less than that dose of amphotericin B or were not treated at all. The median time from onset of neutropenic fever to death was 42 days.

In addition, we are now recognizing late fungal infections in patients who have recovered from neutropenia in acute leukemia. Fever after neutrophil recovery persists in 16% of leukemia-related admissions; 35% of these conditions are due to invasive fungal infections. The study by Talbot and coworkers⁴ has demonstrated that fungal infection is the leading occult cause of fever in acute leukemia after neutrophil recovery. Commonly, the source of the fever is hepatosplenic candidiasis, a previously unrecognized form of invasive fungal disease, now more commonly diagnosed during life as a consequence of the application of imaging techniques to patients with acute leukemia and fever.

These patients have previously been neutropenic but had experienced polymorphonuclear leukocyte recovery; 85% of them have persisting fever, 57% have abdominal pain, and 44% have enlargement of the liver. The serum alkaline phosphatase level is elevated in 60%, and the spleen is frequently enlarged. On imaging studies, 90% of patients will have an abnormality on a CT scan of the liver, 69% on ultrasound of the liver, and 67% on a CT scan of the spleen. These lesions frequently develop a bullseye or target configuration as the host response develops. Biopsy of those lesions demonstrates yeasts, pseudohyphae, and granulomata, although only 42% of biopsy cultures are positive for fungus.⁵

Hepatosplenic candidiasis should be treated with amphotericin B to a cumulative dose of greater than 2 grams until the lesions on a CT scan have resolved or have calcified, or until the liver biopsy has normalized. No patients survive who are treated with total doses equal to or less than 2 grams of amphotericin B; and although the mortality in this condition is 23%, more intensive therapy and better supportive care have been associated with longer survivals. Commonly, flucytosine will be added to the treatment with amphotericin B. Splenectomy may be considered for patients with dominant splenic involvement. Liposome-encapsulated amphotericin B is an investigational therapy which seems to be effective for hepatosplenic candidiasis.

Aspergillosis is another common fungal disease in acute leukemia. *Aspergillus* is ubiquitous in soil, dust, and air. Occasionally, patients with acute leukemia can acquire this infection from occlusive dressings. In the clinical setting, aspergillosis is extremely difficult to diagnosis in patients with acute leukemia. However, the majority of patients will have refractory neutropenic fever, and almost all will have pulmonary infiltrates, 61% of which can be demonstrated to be cavitary on CT scanning.

Extrapulmonary manifestations of aspergillosis are seen less frequently, although in as many as 29% of patients, the brain, liver, spleen, kidney, or heart may contain fungal lesions. The aspergillus organism has the unusual capacity of initiating arterial thromboses, which can secondarily cause infarction and necrosis, and which could underlie the central nervous system disorder manifested by the patient presented here. Blood cultures are almost always negative for fungi; again, treatment in-

volves amphotericin B in a dose of 1–1.2 mg/kg/day.

Prompt neutrophil recovery is essential for survival in aspergillosis, with frequent relapses seen during subsequent courses of aplasia. In fatal cases of aspergillosis, the median time from the onset of neutropenic fever to death was 21 days.

Mucormycosis is a less frequent invasive fungal infection. Mucor organisms are found in soil, dust, and spoiled food. The disease is associated with neutropenia in patients with acute leukemia, as are the other fungal infections, but it occurs particularly in patients with acidosis and hyperglycemia. Patients with mucormycosis will generally present with rhinocerebral disease, usually beginning in the sinuses. The development of pneumonia, and occasionally brain abscess, can accompany mucormycosis. Therapy involves amphotericin B; occasionally, surgery plays a role in treatment of this infection.

Several considerations in the management of invasive fungal disease in acute leukemia deserve comment. First, the choice of effective drugs is small, and the most effective drug, amphotericin B, is associated with substantial toxicity. If it is possible to biopsy an area of suspected fungal infection easily, that procedure should be performed in order to establish the diagnosis. However, most often the accurate diagnosis requires a significantly invasive procedure, so that empiric therapies must often be considered in appropriate patients. Such patients include, for example, those whose neutropenic fever is still refractory after seven days of broad spectrum antibiotic treatment, or in whom recurrent fever develops during neutropenia. These latter patients should be considered for treatment with amphotericin B, initially with the usual test dose and then escalated to 0.3–0.6 mg/kg/day by the second or third day of treatment.

Those patients whose pulmonary infiltrates during neutropenia remain refractory to antibiotic treatment and whose fungal cultures are persistently negative should be considered for amphotericin B treatment in a dose of 1 mg/kg/day. The study at the University of California at San Francisco³ has shown that such empiric antifungal therapy yields effective clinical results in 74% of those patients who are suspected of invasive fungal disease but whose infections remain undiagnosed. This empiric approach involves unnecessary therapy for 40% of patients subsequently discovered to be uninfected, but who happen to fit the clinical algorithm; clearly empiric therapy is justified, however, to save those patients whose fungal illnesses are difficult to diagnose during life.

In addition to amphotericin B, adjunctive therapies include resection of the residual fungoma, splenectomy in splenic-dominant hepatosplenic candidiasis, and the addition of flucytosine, especially with *C tropicalis* infections.

The optimal duration of antifungal therapy is unknown. However, if patients are treated with empiric therapy for neutropenic fever, amphotericin B is usually discontinued with the appearance of neutrophil recovery. For culture-positive infections, most clinicians administer a total dose of 15–20 mg/kg of amphotericin B. Hepatosplenic candidiasis, however, requires a total dose of amphotericin B of greater than 2 g, as guided by imaging studies and biopsies. If the patient harbors an intravascular device that is suspected of contributing to the fungal infection, such a

patient may be offered a brief course of amphotericin B after removal of the device.

Prophylactic antifungal therapy with miconazole or other similar agents is used in some medical centers. The role of fluconazole in the definitive treatment of invasive fungal infection in acute leukemia is entirely speculative, as this agent has only recently received FDA approval.

The prognosis of patients with invasive fungal infection in acute leukemia is best illustrated by the series of 54 patients reported from Milan, with hematologic malignancies and documented invasive fungal disease.⁶ All of these patients had had neutropenic fever, with approximately equal numbers of invasive candidal and invasive aspergillus infections. Fifty-seven percent of the patients were treated with amphotericin B on an empiric basis using a protocol algorithm; all 42% of those patients who were cured had demonstrated neutrophil recovery. Fifty-eight percent of the group treated with amphotericin B by protocol died, but only 17% of this group of fatal cases had experienced neutrophil recovery. Forty-three percent of the total group of patients either were not treated with amphotericin B, received an inadequate dosage of this drug, were given "late treatment," or were diagnosed at autopsy; all of these patients died.

This series underscores the fact that there are two essential ingredients to survival in patients with invasive fungal disease. These are prompt and adequate treatment with amphotericin B, and effective recovery of polymorphonuclear leukocytes from a neutropenic status.

In summary, invasive fungal disease is common during and following neutropenia in patients with acute leukemia. The condition is extremely difficult to diagnose and requires a high index of suspicion on the part of the clinician. Because of the high mortality and morbidity of these invasive fungal diseases, affected patients must commonly be treated empirically to avoid a fatal outcome.

This patient had abdominal discomfort and persisting and progressive disease after neutrophil recovery in the setting of prolonged neutropenia, steroid therapy, and treatment with broad spectrum antibiotics. We were able to demonstrate rare mycelial elements in the brain, pulmonary infiltrates, hepatic defects on CT scan, and an elevated serum alkaline phosphatase level. The most appealing diagnosis here is hepatosplenic candidiasis. The study reported from the M. D. Anderson Hospital¹ appears to predict that a diagnosis in this patient would have been made by bronchoscopy.

Although extensive disseminated disease, as in this patient, is less frequently associated with *Aspergillus* infection, aspergillosis must be strongly considered here, especially since this patient presented with a central nervous system event compatible with ischemic infarction.

CLINICAL DIAGNOSES

Acute lymphocytic leukemia—status post induction therapy.

Disseminated fungal infection complicating neutropenia—hepatosplenic candidiasis? Aspergillosis?

PATHOLOGY PRESENTATION

Harlan D. Alpern, MD (Pathologist-in-Chief): The patient's peripheral blood smear at the time of admission

demonstrated a white blood cell count of 36,300 cells/ μ L. Ninety-eight percent of the white cells were lymphocytes, most of which were large lymphocytes with high nuclear-to-cytoplasmic ratios and with prominent nucleoli; many nuclei were clefted. The aspirate of Wright's-stained bone marrow was highly cellular, demonstrating large numbers of these immature lymphoid forms. A bone marrow biopsy disclosed a cellularity estimated at 90%; the normal hematopoietic elements were overrun by sheets of immature lymphoid cells. Based on the results of immunophenotyping, this malignant lymphoid disorder was classified as acute lymphoblastic leukemia, early B-cell type.

Subsequently, a bronchial biopsy was performed, which demonstrated abundant blood within alveolar air spaces and thickening of alveolar septal walls. Appropriately stained sections demonstrated no organisms and there was no evidence of leukemic infiltration.

Following chemotherapy, a repeat bone marrow biopsy was performed, demonstrating low cellularity and no evidence of recurrent leukemia. Following the onset of cerebral symptoms, biopsy of the left temporal lobe was performed and disclosed extensive necrosis and cerebritis. In a single focus in the brain, a section stained by the Gomori methenamine silver (GMS) method demonstrated a small aggregate of fungi, which could not be classified on the basis of the few organisms seen.

At postmortem examination, the lungs were of normal weight. In the left upper lobe there were multiple small nodular cystic lesions; in the right upper lobe, which was extensively atelectatic, there was a cystic lesion 1.2 cm in diameter which contained caseous material (Fig 2). On histologic evaluation, these lesions were found to be abscesses involving bronchi and pulmonary parenchyma, and were composed of sheets of polymorphonuclear leukocytes with adjacent granulation tissue. Within the abscesses were fungal colonies (Fig 3). The hyphal forms demonstrated acute-angle branching and septae typical of *Aspergillus* (Fig 4).

The liver was slightly enlarged and contained two abscesses greater than 2 cm in diameter, as well as multiple small abscesses. *Aspergillus* organisms were histologically identified within these hepatic abscess cavities. Chronic pancreatitis was present, with interstitial fibrosis and acinar atrophy. Pancreatic islets demonstrated deposition of amyloid typical for type 2 diabetes mellitus. The kidneys were enlarged, at 240 and 210 grams. There was hyaline arteriosclerosis with concomitant diffuse glomerulosclerosis, both of which are attributable to diabetes mellitus. There was a clinical history of hypertension which is attributable to the hyaline arteriosclerosis. In the kidneys, there were multiple small abscesses that contained aspergillus. The thyroid gland was slightly enlarged; the left lobe was the site of a colloid nodule, within which was an abscess containing aspergillus.

The heart was enlarged at 440 grams. There was moderate coronary atherosclerosis, myofiber hypertrophy, and a small focus of fibrosis of a left ventricular papillary muscle. The enlarged heart was attributed to coronary atherosclerosis and hypertension. The bone marrow was cellular, with all three hematopoietic lines demonstrating maturation in appropriate numbers and without evidence of recurrent leukemia.



FIGURE 2. Multiple *Aspergillus* abscesses in right lung (typical lesion at upper arrow); *Aspergillus* abscess-cyst containing caseous material (lower arrow).

The brain was of normal size. In the left temporal lobe there was an abscess that measured 3 cm in maximum dimension. In the left centrum semiovale was a soft gray focus 3 mm in maximum dimension. On histologic examination, both lesions demonstrated necrosis, cerebritis, and aspergillus colonies. Occasional thrombosed vessels were present. The vascular thrombi that occur in disseminated aspergillosis are responsible for ischemic necrosis.

Invasive aspergillosis occurs most often in immunocom-

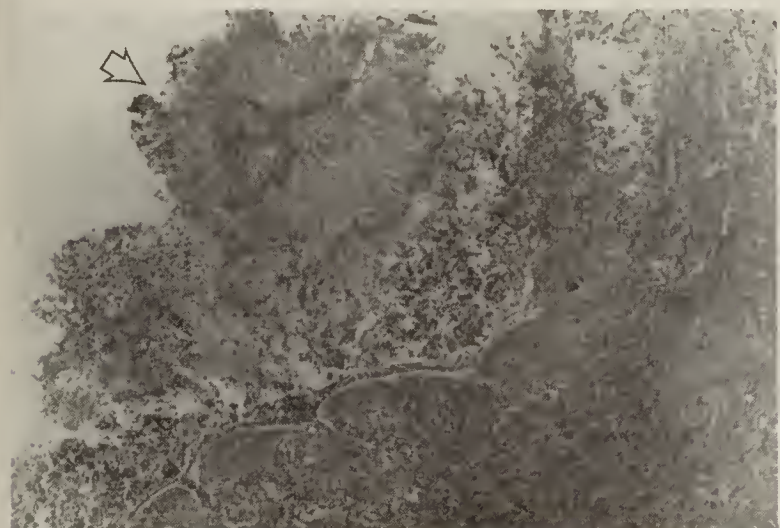


FIGURE 3. *Aspergillus* fungal colony (at arrow) in pulmonary abscess (hematoxylin-eosin stain; original magnification $\times 40$).

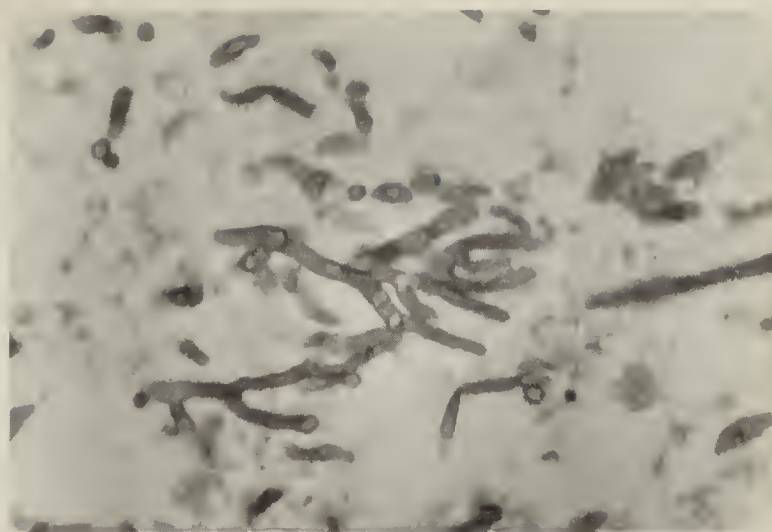


FIGURE 4. *Aspergillus* hyphae with acute-angle branching and septae (hematoxylin-eosin stain; original magnification $\times 400$).

promised individuals. Patients with underlying acute leukemia and severe granulocytopenia are especially susceptible, but this invasive fungal infection can occur in individuals with a variety of other malignant or debilitating diseases and in patients receiving immunosuppressive medication. The lungs are the primary site of infection, generally by inhalation of airborne spores. *Aspergillus* is a ubiquitous organism, found in soil, decaying vegetation, and organic debris. *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, and *Aspergillus terreus* are the species involved. Histologically, *Aspergillus* is characterized by septate mycelia that average four micra in diameter and have branches at 45 degree angles.

In summary, this patient, a 65-year-old woman, died of disseminated aspergillosis, in a setting of neutropenia occasioned by chemotherapy, which had induced remission of acute lymphoblastic leukemia.

FINAL DIAGNOSES

Disseminated invasive aspergillosis, involving lungs, brain, liver, kidneys, and thyroid.

Acute lymphoblastic leukemia, in remission.

Moderate coronary atherosclerosis, with cardiac hypertrophy.

Diabetes mellitus.

Hyaline arteriolosclerosis and diffuse glomerulosclerosis, involving the kidneys.

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Fatal hemoptysis in lymphangiomyomatosis

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Massive hemoptysis is commonly defined as pulmonary hemorrhage of more than 600 mL of blood in 48 hours. The common causes are tuberculosis, bronchiectasis, lung abscess, and lung cancer. Mortality from massive hemoptysis ranges from 50% to 100%.¹

Pulmonary lymphangiomyomatosis is a rare, progressive disease of unknown cause. It occurs almost exclusively in women of reproductive age and is characterized by widespread proliferation of muscle throughout the lungs.² The chief complaint of these patients is usually dyspnea. Pneumothorax, minimal hemoptysis, and chylothorax are common complications.^{3,4} Fatal hemoptysis as an early presenting manifestation, to our knowledge, has not been previously reported in the literature.

CASE REPORT

A 37-year-old woman presented to the emergency room with massive hemoptysis. She had had three uncomplicated pregnancies, the last one being 14 years before, and had undergone a hysterectomy five months prior to admission at which time leiomyomata were found. No chest x-ray was done at the time. She also had a history of normocytic normochromic anemia. Bone marrow examination prior to hysterectomy was reported normal. The patient was in good health until two months before admission, when she presented to her local physician complaining of mild dyspnea on exertion. A chest roentgenogram done at that time was normal.

On the day of admission, she was able to work. While commuting home, massive hemoptysis and shortness of breath developed.

On physical examination, the patient was found to be a well-developed, well-nourished woman in severe respiratory distress. Her blood pressure was 120/70 mm Hg; pulse

rate, 120/min; respiratory rate, 40/min; and temperature, 98°F. The chest examination revealed bilateral diffuse inspiratory crackles. The rest of the physical examination was unremarkable.

Laboratory studies disclosed a hemoglobin of 11.4 g%, white blood cell count, 10,000/mm³, and normal platelet count. Arterial blood gas studies on 4 liters oxygen flow via nasal cannula revealed the following: pH 7.23; PaCO₂, 30 mm Hg; and PaO₂, 30 mm Hg. Serum sodium was 139 mEq/L; potassium, 3.6 mEq/L; chloride, 107 mEq/L; bicarbonate, 12 mEq/L; and glucose, 355 mg/dL. A test for acetone was negative. The prothrombin and partial thromboplastin times were normal. The electrocardiogram showed a sinus tachycardia. The chest roentgenogram revealed a bilateral, diffuse interstitial and nodular-acinar pattern (Fig 1).

The patient required intubation and mechanical ventilation with high inspired oxygen concentrations, and she received two units of packed red blood cells. Bronchoscopic examination revealed blood in the entire tracheobronchial tree and apparent fresh bleeding from the superior segment of the left lower lobe.

Endobronchial management of the hemoptysis was done via a Fogarty catheter placed in the left lower lobe. Her gas exchange improved; the bleeding ceased but recurred after 24 hours. A repeat bronchoscopy showed blood throughout the tracheobronchial tree. The patient's gas exchange worsened. Bronchial artery arteriography with possible gel-foam embolization was planned. However, her gas exchange contin-

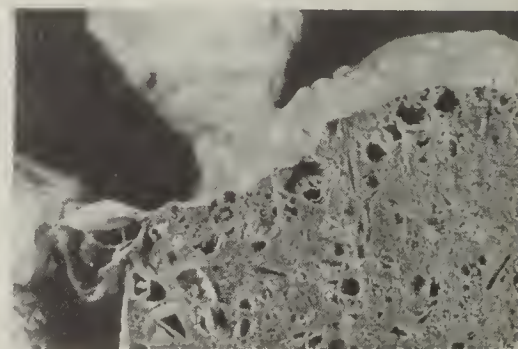


FIGURE 2. Close-up photograph of lung showing abnormal cyst-like spaces with thick intervening walls, resembling honeycombing.

ued to deteriorate, and the patient died, despite vigorous resuscitative measures.

At autopsy, the lungs were voluminous with subpleural cyst formations up to 1.0 cm in diameter (Fig 2). They were hemorrhagic and showed areas of honeycombing in all lobes. Some of these spaces contained dark blood, especially the ones located at the bases of the upper lobes and superior segments of the lower lobes. The regional lymph nodes had reddish-black cut surfaces. Microscopic examination of the lungs showed diffuse, multiple nodular, interstitial proliferations of the smooth muscle in the lobular septa, pleura, alveolar walls, and in the walls of bronchioles and small bronchi. Similar proliferation was present in the walls of pulmonary veins (Fig 3) and lymphatic channels, which were dilated. In many areas, subpleural cysts were filled with blood. The alveoli were filled with edematous fluid and/or blood and hemosiderin-laden macrophages. These changes are characteristic of lymphangiomyomatosis (LAM). Mediastinal lymph nodes also re-



FIGURE 1. Chest film with endotracheal tube in place shows bilateral, diffuse interstitial disease process with honeycombing.

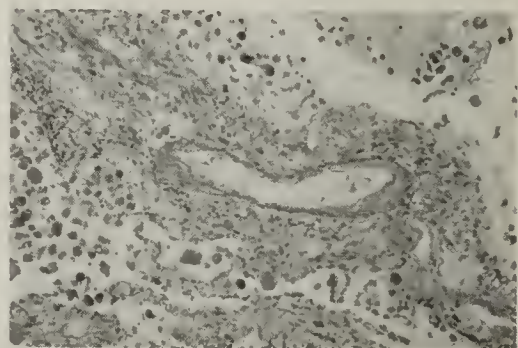


FIGURE 3. Elastic Van Gieson stain identifies a vein, the wall of which is being encroached on by proliferating leiomyocytes (original magnification $\times 100$).

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vealed changes consistent with LAM. There was no other organ involvement.

DISCUSSION

Pulmonary lymphangiomyomatosis is an uncommon disease that occurs primarily in women of child-bearing age.^{3,4} Fewer than 100 women with this condition have been described.⁵ LAM is a part of a systemic disorder caused by widespread proliferation of smooth muscle in the pulmonary lymphatics, venules, and smaller airways, and in mediastinal and retroperitoneal lymph nodes and lymphatic vessels.^{2,6} LAM commonly presents with progressive dyspnea. Recurrent spontaneous pneumothorax and chylous pleural effusions are other initial identifying features.^{3,4} Chest roentgenograms, if abnormal, typically reveal a diffuse interstitial pattern more marked at the bases, and/or hyperinflation, pleural effusion, and pneumothorax. Computed tomography (CT) reveals multiple diffuse lung cysts despite normal chest roentgenograms and other multisystemic abnormalities.^{5,6} Pulmonary function studies show a mixed obstructive and restric-

tive pattern with a notably severe reduction of the diffusing capacity.^{3,6} Therapy has been generally unsatisfactory and mostly palliative. However, successful treatment with oophorectomy and progesterone has been reported.⁷

Hemoptysis has been reported as a frequent complication of lymphangiomyomatosis and usually occurs late during the course of the disease.^{3,8} It is often recurrent, presenting as blood-streaked sputum or frank hemoptysis. In a review of 67 patients with lymphangiomyomatosis reported by Carrington et al,³ hemoptysis developed in 40% during the clinical course of the disease. Hemoptysis has rarely been reported as an early manifestation of lymphangiomyomatosis.⁹ Massive, nonfatal hemoptysis that occurred three years after the diagnosis of lymphangiomyomatosis was reported by Carrington et al.³ To our knowledge, massive, fatal hemoptysis as the presenting symptom has not been reported in the literature thus far. The usual cause of death is progressive respiratory failure that occurs within ten years of diagnosis.² Although the specific bleeding site

in this patient could not be ascertained, based on the pathologic findings we speculate that hemoptysis was the result of diffuse obstruction of the pulmonary venules, and that the roentgenographic abnormality resulted from the subsequent hemorrhage.

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Localized fibrous tumors of the pleura:

Report of two cases, benign and malignant

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Localized mesothelioma of the pleura has long been a poorly understood entity. While its precise histogenesis has not yet been fully elucidated, localized mesothelioma is distinguishable from diffuse malignant mesothelioma. Diffuse mesothelioma is more common, and almost invariably has a poor prognosis. Moreover, as its name implies, it originates from the mesothelial cell. In contrast, localized mesothelioma is often benign and has a more favorable clinical course. Consequently, it is important to differentiate these two entities.

The most basic difference concerns

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the presumed cellular origin for localized pleural tumors. Several early studies^{1,2} suggested a mesothelial origin. However, more recent ultrastructural and immunohistochemical evidence strongly suggests a submesothelial fibroblastic origin for these neoplasms.³⁻⁵ Although the vast majority of localized fibrous pleural tumors are benign, malignant variants have occasionally been described.^{6,7} In this paper we report two cases of localized mesothelioma of the pleura, one benign, the other malignant.

CASE REPORTS

Case 1. A 67-year-old woman had a three-month history of sneezing, congestion, shortness of breath, and nonproductive cough. A chest radiograph revealed a large, well-circumscribed mass involving much of the left hemithorax (Fig 1). History, physi-



FIGURE 1. Posteroanterior roentgenogram of the benign localized fibrous pleural tumor.

cal examination, and laboratory studies were noncontributory. The patient denied tobacco use. No clubbing of the extremities was noted. A thoracotomy was performed, and a 25 × 15 × 10-cm, multilobulated tu-

mor was found; the vascular supply arose from a pedicle in the lower portion of the mass.

On gross examination, the tumor was fibrous in consistency. The cut surface presented a firm, nodular appearance. A stalk, measuring 1.5 cm in diameter, was noted. Microscopic examination (Fig 2) showed the neoplasm to be composed of spindle-shaped cells with plump nuclei. The cytoplasm was abundant and faintly eosinophilic. The cells showed no obvious pattern or formation. The tumor was less cellular in areas, appearing more collagenized, with focal necrosis and some dystrophic calcification. The cells showed no evidence of anaplasia, pleomorphism, or mitotic activity. The tumor was highly vascular; the stalk was composed of thick-walled blood vessels and sparse spindle-shaped cells. The tumor had compressed the lung parenchyma at the periphery.

Immunoperoxidase staining for cytokeratin was performed on paraffin-embedded tissue using a combination cocktail of mouse monoclonal antibodies specific for cytokeratin (#MA-902, Enzo Biochem, New York, NY; #0702, Hybridtech Inc, San Diego, CA; and #7650, Becton-Dickenson, Mountainview, CA) and vimentin (#M725, Dako Corp, Santa Barbara, CA). Immunohistochemical studies using these methods showed the cells to be vimentin positive and cytokeratin negative.

Case 2. A 78-year-old woman was admitted with a one-year history of fever of unknown origin, a lung mass in the right lower lobe, exertional dyspnea, and syncopal episodes secondary to hypoglycemia. Additionally, her pulmonary function tests revealed a restrictive pattern. Her medical and surgical history were unremarkable. Clubbing was noted on physical examination.

Laboratory studies were remarkable for a serum glucose level ranging from 64 to 75 mEq/L. Radiographic examination of the chest showed a mass in the right lower lobe partially obscuring the right hemidiaphragm (Fig 3). Hypertrophic pulmonary osteoarthropathy was noted to be present on bone scan. A thoracotomy was performed, and the tumor was completely resected. The extremely vascular pedicle of the tumor was

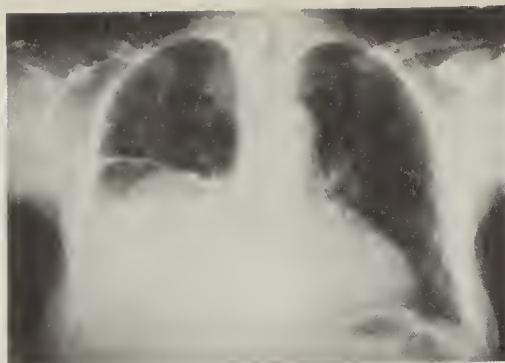


FIGURE 3. Posteroanterior roentgenogram of the malignant localized fibrous pleural tumor.

attached to the central tendon of the diaphragm, and the mass showed several dense adhesions to the lung. Additionally, several hundred cubic centimeters of serous fluid was present in the pleural cavity.

The tumor measured 22 × 20 × 6 cm. The external surface was lobulated, and the cut surface had a nodular and cystic appearance with focal areas of hemorrhage. On microscopic examination, the tumor was composed of spindle-shaped cells (Fig 2, right); the cellularity was more pronounced in areas. Prominent vascularity was present. The cellular areas alternated with more loosely edematous areas, in which nuclear pleomorphism and anaplasia were evident. These areas were mitotically active (average 7/10 per high power field) and showed many abnormal mitotic forms. Occasional bizarre giant cells were present, as were large areas of tumor necrosis. The neoplasm had invaded the lung parenchyma and bronchial structures. Immunohistochemical studies, using the same techniques described in case 1, showed the tumor cells to be vimentin positive and cytokeratin negative.

DISCUSSION

Localized tumors of the pleura usually occur in people over 40 years of age and show a slight female preponderance. The majority are asymptomatic and are discovered on routine radiographic examination of the chest. In patients who become symptomatic, cough, chest pain, dyspnea, clubbing,

hypertrophic pulmonary osteoarthropathy, chills, and fever have all been reported.⁷ Malignant forms tend to recur and display locally invasive behavior but rarely metastasize. The malignant nature of the tumor in the second case was suspected based on clinical evaluation and was confirmed on microscopic examination. Histologically, there was marked anaplasia with nuclear pleomorphism, prominent and abnormal mitotic activity, and tumor necrosis. There were no clinical or pathologic features to suggest malignancy in the first case, and the patient was well 15 months after surgery. In the second case, although the follow-up period was admittedly short, the patient showed no evidence of recurrence or metastatic disease 24 months after surgery.

Immunohistochemical studies in both cases support a submesothelial fibroblastic origin for these neoplasms. The tumor cells from both cases were vimentin positive and cytokeratin negative. In general, vimentin is a marker of mesenchymal cells, whereas cytokeratin is associated with mesothelial and epithelial cells. Cytokeratin is almost uniformly positive in diffuse malignant mesothelioma.⁶ Consequently, these immunohistochemical results support a fibroblastic (mesenchymal) rather than a mesothelial cellular origin for these two neoplasms.

In fact, there is much evidence in the literature to support a mesenchymal origin for the benign variety of localized pleural tumors.³⁻⁷ However, a mesenchymal origin for malignant localized pleural tumors has been less well documented. It is likely that the malignant tumor reported here is analogous to the spindle-cell sarcoma and the localized fibrous malignant mesothelioma described in other studies.^{6,7}

In light of the more favorable prognostic outlook for the benign variety of this lesion compared to diffuse malignant mesothelioma, and the likely mesenchymal origin for its benign and malignant variants, it seems appropriate to avoid referring to these tumors as mesotheliomas. Nomenclature that more accurately reflects the probable origin of these neoplasms would avoid confusion with the more common diffuse malignant pleural mesothelioma, and is probably more appropriate. In this regard, the terms localized benign fibrous pleural tumor³ for the benign type, and localized spindle-cell sarcoma or localized malignant fibrous pleural tumor⁷ for the malignant variant, would more precisely reflect the prognosis and cel-

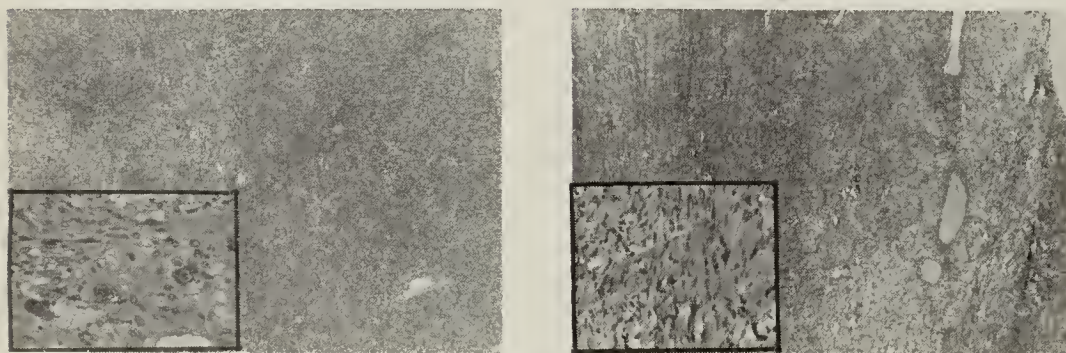


FIGURE 2. Left, Microscopic appearance of localized benign fibrous pleural tumor. Note the bland spindle-shaped cells, stromal collagen, and rich vascularity (hematoxylin-eosin stain; original magnification × 450). Inset, high power appearance of spindle cells. Right, Microscopic appearance of localized malignant pleural tumor. Note the highly cellular nature of the neoplasm. The inset shows the anaplastic tumor giant cells present in the more loosely arranged area (hematoxylin-eosin stain; original magnification × 450).

lular origins of these tumors, and may represent more reasonable alternatives.

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Endometriosis of the rectum treated with a long term GnRH agonist and surgery

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MARK J. SNELL, MD

Endometriosis is a common disease with a reported incidence rate of 10-15% among women undergoing pelvic surgery.¹ Extrapelvic disease is considerably less common than disease of the pelvis itself, and frequently is more difficult to diagnose because the presenting symptoms are shared with other more common pathologic processes. The etiology of endometriosis is unclear. Its occurrence may represent a multifactorial event including the classic theories of development, along with an altered immune response among affected women.

Pelvic and extrapelvic endometriosis can be managed via a variety of approaches: expectant management, medical management, conservative surgery, definitive surgery, or combined therapy.² Though data are becoming available on optimal care of pelvic endometriosis,³⁻⁵ relatively little data are available concerning the treatment of extrapelvic disease.⁶ We report here a patient with endometriosis of the rectum (Class I, Stage II2b)⁶ who was evaluated over an extended period of time at another facility. Following this, prolonged GnRH agonist (leuprolide acetate) therapy was instituted at this facility, followed by surgery, with good

results and with preservation of reproductive function.

CASE REPORT

A 29-year-old nulliparous woman presented to a primary care clinic at another facility in December 1986 because of complaints of rectal bleeding, pressure, and constipation. The symptoms, though not exclusively related to menses, were frequently more common in the premenstrual and menstrual periods. There was no family history of colon or pelvic disease. Pelvic examination at the time of the first clinic visit was reported as unremarkable, and a stool guaiac test performed then was negative. During an annual physical examination in January 1987, a rectal mass was found, and the patient was referred to this hospital for consultation.

A radiographic study with barium enema was performed in March 1987, and showed two small rectal lesions. A gastroenterological consultant recommended colonoscopy, which for undetermined reasons was not performed until July 1987. At the time of colonoscopy, a 3 cm to 4 cm flat, sessile, fungating mass was visualized at 6 cm to 8 cm in the rectum. No polyps were seen, and no other pathologic findings were noted. A biopsy was attempted, but was considered inadequate. The pathology report indicated "mild edema and chronic inflammation." The patient was then referred for surgery and was admitted to the hospital for evaluation.

A computed tomographic (CT) scan and magnetic resonance imaging (MRI) were done (Fig 1), both depicting a rectal mass in the area of the previously visualized lesion. A repeat colonoscopy was carried out, with additional biopsies which were read as "fragments of benign colonic mucosa showing submucosal benign endometriosis." The pathology report further described an extension of the endometriosis "to the deepest as-

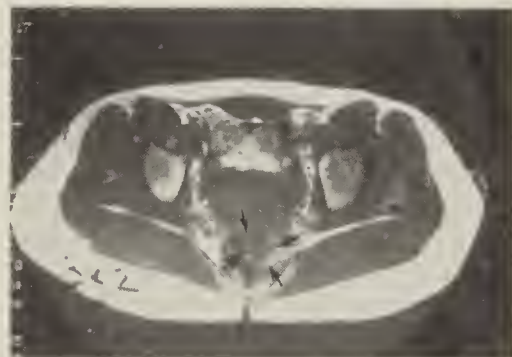


FIGURE 1. MRI T1 image of lower pelvis showing endometriotic lesion in the anterior wall of the rectum.

pect of the biopsy suggesting an extension of the process from the serosa to the submucosal region of the rectum."

The patient was placed on danazol, 800 mg per day, which she continued to take from August 1987 to March 1988, with good suppression of her symptoms. A first menses after danazol therapy occurred in April 1988, and shortly after that, the patient noted a recurrence of rectal bleeding, constipation, and pelvic pressure. Rectal and pelvic examinations noted no increase in the size of the rectal lesion, and the patient expressed a strong desire to avoid surgical intervention until all other options were exhausted. All options of medical, surgical, and combined management were reviewed with the patient and, at her request, medical suppression was reinstituted using leuprolide acetate, 1.0 mg subcutaneously daily. The symptoms subsided within 30 days after initiation of this regimen, and the patient became completely asymptomatic while on suppressive therapy.

The patient was first seen in the Reproductive Endocrinology Clinic of this hospital in January 1989, after having been on leuprolide acetate for six months. The leuprolide acetate was continued beyond the usual six-month management period because of a

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The opinions expressed herein are those of the authors and are not necessarily those of the United States Air Force or the Department of Defense.

decrease in the size of the rectal mass from a 3–4 cm lesion to a 2–3 cm lesion, the complete absence of symptoms, and the patient's desire to avoid surgery.

In March 1989, the patient's condition was reassessed using serial pelvic examinations, chemistry panel, and dual photon absorptiometry. The rectal mass was found unchanged at 2–3 cm. The chemistry panel was within normal limits. The bone mineral studies indicated a slightly reduced trabecular bone mass in the lumbar spine (11% below the mean) when compared to age, weight, and sex-matched controls. No change was noted in cortical bone content determined from the shaft of the radius. The patient was placed on low dose conjugated estrogen, 0.3 mg/day, to prevent further trabecular bone loss. No recurrence of symptoms occurred on the estrogen replacement therapy.

In spite of the patient's symptom-free status, it was thought that the indefinite use of GnRH agonist treatment was not supported by the medical literature. The rectal mass appeared to have reached a plateau without further reduction in size, indicating the possibility of an endometrioma. The patient therefore underwent surgery in September 1989, during which laparoscopy was performed revealing no evidence of active pelvic endometriosis. The uterus and fallopian tubes appeared normal. However, both ovaries were small (1 × 2 cm) and appeared immature secondary to the prolonged suppression. A perirectal mass was noted in the posterior cul-de-sac measuring 2 × 3 cm and located somewhat to the left of midline. A laparotomy was accomplished two days later, and an anterior resection was carried out, removing a segment of rectum including the entire rectal lesion. The rectum was repaired with an end-to-end anastomosis stapler (Disposable Premium CEEA staplers, United States Surgical Corp). The specimen revealed a 2 × 3-cm firm mass in the anterior rectal wall just to the left of midline. Microscopic examination indicated an endometrioma of the rectum (Fig 2).

The patient did well after surgery; she remained in the hospital for 11 more days because of a postoperative ileus which resolved spontaneously. She remained on leuprolide acetate for an additional three months, at which time her menstrual periods were al-

lowed to resume. A first normal period occurred in March 1990, and at the patient's six-month postoperative examination, she was free of complaints. A pelvic and rectal examination revealed no evidence of recurrence. The patient will be followed at six-month intervals for the next two years. She has been started on oral contraception at her request.

DISCUSSION

The etiology of pelvic or extrapelvic endometriosis remains unclear. Several factors play a role in the onset of macroscopic disease: These include the classic theories of retrograde menstruation, vascular and lymphatic passage of endometrial fragments, and coelomic metaplasia combined with an altered immune response in patients presenting with the disease.^{7,8} It is also quite possible that endometriosis exists in two forms, microscopic⁹ and macroscopic, and that all women have microscopic endometriosis at one time or another, but only 10% to 15% develop classic macroscopic disease diagnosed at pelvic surgery. The difference between one group and the other may result from multiple factors including genetic make-up, race, menstrual cycle, child-bearing history, outflow obstruction, and hormone levels,¹⁰ with the most important factor being an altered cellular immunity.¹¹

Extrapelvic endometriosis differs from pelvic disease only in the location of involvement. There are no data to suggest that there is a difference in etiology, progression, or response to current management regimens. Pelvic endometriosis has been defined as a disease of the uterus, fallopian tubes, ovaries, and adjacent peritoneum. Extrapelvic endometriosis has been defined as endometriosis of all other organs and tissues including the urinary bladder, sigmoid colon and rectum, and the vagina.² Extrapelvic endometriosis has been conveniently divided into four classes: endometriosis of the intestinal tract, of the urinary tract, of the lung and thoracic cage, and of other sites.² A new classification of extrapelvic endometriosis has recently been proposed, further dividing the disease into organ defect involvement, extrinsic and/or intrinsic disease, and the size of involvement.⁶ Like the revised staging system of the American Fertility Society (1985), which applies only to pelvic disease, such a new classification and staging system may in the future simplify the process of assessment of extrapelvic endometriosis.

Intestinal endometriosis represents

the most common area of extrapelvic endometriosis, with the sigmoid colon and rectum the areas of greatest involvement. The most common presenting complaints include abdominal and pelvic pain, abdominal distention, rectal bleeding, and diarrhea or constipation among women in the reproductive age group.² It is our impression that all patients with known or suspected extrapelvic endometriosis should undergo a diagnostic laparoscopy to assess adequately the pelvic component of their disease. This is supported by the observation that most cases of extrapelvic endometriosis (involving the gastrointestinal tract, urinary tract, lung, and thoracic cage) have concurrent disease.² Conversely, all patients with pelvic endometriosis who have cyclic symptoms of dysfunction of other organs of the body should be suspected of having extrapelvic disease. Previous data suggest that intestinal endometriosis is best managed with medical suppression, provided obstruction does not exist.⁶ If obstruction occurs, or if the disease does not respond to medical management or recurs after medical management, then surgical intervention has been the treatment of choice. It has been our observation that surgical intervention is less complicated when presurgical medical suppression has been instituted.

In the case presented here, the patient initially complained of symptoms of rectal bleeding, pressure, and constipation, which led to a diagnosis of rectal endometriosis without obstruction. Options for management were presented to the patient and, because of her desire to avoid surgery, she was treated by medical suppression. Ovarian steroidogenesis was initially suppressed with danazol for eight months, followed by the GnRH agonist leuprolide acetate for 16 months, resulting in complete suppression of presenting symptoms and an initial reduction in the size of the rectal lesion. It should be noted, however, that symptoms recurred after the danazol suppression was discontinued. The GnRH agonist was then instituted because of the continued desire of the patient to avoid surgery. Because of the lack of data relating to complications of prolonged GnRH agonist administration and the concern over the side effects of continued ovarian suppression, serum chemistry studies and bone density assessments were accomplished, and after 16 months of leuprolide therapy laparoscopy was carried out, followed by laparotomy with resection of

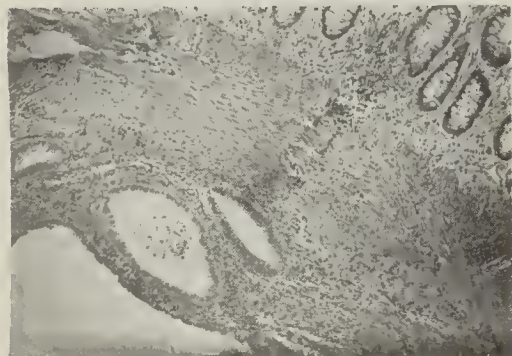


FIGURE 2. Microscopic section of endometriosis of the anterior rectal wall showing both rectal mucosa and endometrial glands (original magnification ×100).

the rectal lesion and an end-to-end reanastomosis.

The utilization of low dose estrogen replacement therapy during the last four months of GnRH agonist administration was instituted in an attempt to minimize additional trabecular bone loss during the extended treatment regimen. It should be noted that the addition of low dose replacement therapy during GnRH agonist management has been entertained by several groups. However, the benefits have not been proven by appropriate studies to date. Of concern is the fact that the post-treatment laparoscopy revealed no evidence of active pelvic endometriosis and, since laparoscopy was not performed at the time of initial diagnosis, the possibility exists that the patient only had active rectal disease.

This case represents the interesting but frustrating problem of a patient who received care from several different facilities, with institution of a management plan prior to complete evaluation. As a result of this, it was necessary to develop a management plan that in-

corporated the completed evaluation and that extended medical suppression with surgical intervention in a manner different from current protocols. The medical suppression was extended because of favorable results and because of the patient's desire to avoid surgical intervention. The diagnostic laparoscopy was accomplished at a different time from the definitive surgery to authenticate the extent of her current disease and to accomplish adequate planning and preparation for the surgical procedure.

This case also serves to support the impression that suppression of ovarian steroidogenesis may be effectively utilized in managing extrapelvic endometriosis for longer periods than the currently advised six-month regimens. This can be done provided the patient is carefully monitored for risk factors of hypoestrogenism such as osteoporosis, and if it is thought that such an extension would result in further reduction in the size of lesions. Such a therapeutic plan may permit a less radical surgical procedure in cases of rectal endometri-

osis, obviating a colostomy and total abdominal hysterectomy with bilateral salpingo-oophorectomy.

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Erythromelalgia: A rare cause of extremity pain

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Erythromelalgia is a rare syndrome characterized by pain, redness, and increased skin temperature of one or more extremities. Case reports of this entity date back to the 19th century. Erythromelalgia was first described by Mitchell,¹ who used the term erythromelalgia based on Greek derivatives: *erythros* (red), *melos* (extremities), and *algos* (pain). Smith and Allen² were the first to classify the condition as either primary (idiopathic) or secondary (related to underlying hematologic, vascular, or systemic disease). Because of increased extremity skin temperature they coined the name *erythromelalgia*, which is also used to describe the condition.

We present a case of secondary

erythromelalgia with several interesting features: extremity involvement was unilateral, with a unique ulnar nerve distribution in the presence of an underlying myeloproliferative syndrome. The lesion resolved promptly after treatment with aspirin.

CASE REPORT

An 80-year-old man presented to the hospital with a six-month history of progressive fatigue, malaise, anorexia, and a 30-pound weight loss. Prior to the onset of symptoms the patient had been in good health with only a history of borderline hypertension and kidney stones.

Complete blood studies revealed a hemoglobin and hematocrit of 8 g/dL and 24.2%, respectively, and a leukocytosis of $45.0 \times 10^9/L$ with 73% segmented neutrophils, 23% band forms, 2% monocytes, 1% metamyelocytes, and no lymphocytes. Platelets were markedly elevated at 1,705,000. The peripheral smear revealed red cell anisocytosis, mild fragmentation, neutrophilic toxic granulation, and an occasional large platelet.

Further work-up included chest and abdominal computerized axial tomographic (CAT) scans which were negative. A skeletal survey was within normal limits. A profile-12 examination was normal, save for an elevated lactic dehydrogenase level of 588 U/L. The erythrocyte sedimentation rate was normal, while there was an elevated leukocyte alkaline phosphatase score of 326 (normal, 13-130). Serum protein electrophoresis testing revealed the presence of a monoclonal IgG of 2,340 mg/dL without depression of IgA or IgM.

A bone marrow aspiration and biopsy revealed a hypercellular marrow with granulocytic and megakaryocytic hyperplasia, a myeloid-erythroid ratio of 8:1, rare ringed sideroblasts, and many atypical and bizarre megakaryocytes (Fig 1). Plasma cells were moderately increased (10% to 15%) without atypical or immature forms. There was no evidence of metastatic carcinoma or myelofibrosis. The findings were consistent with a diagnosis of myeloproliferative syndrome.

One week after admission, the patient noted sudden onset of pain, erythema, and warmth of the lateral aspect of the right

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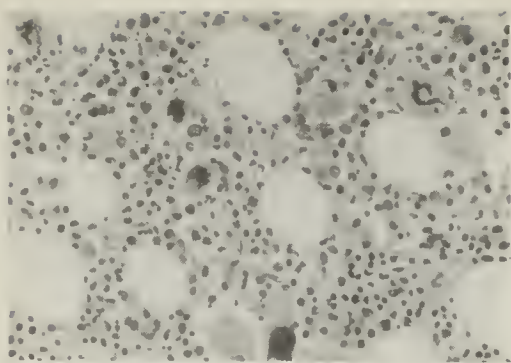


FIGURE 1. Bone marrow biopsy showing hypercellularity with granulocytic and megakaryocytic hyperplasia (hematoxylin-eosin stain; original magnification $\times 1,000$).

hand (Fig 2). The physical findings on the right hand were in the pattern of the ulnar nerve distribution. The erythema blanched with pressure and then promptly returned to its reddish color. Other pertinent findings included bounding radial and ulnar pulses with a negative Allen test. Sensation was normal at all sites on the right hand.

Because of the physical findings and underlying myeloproliferative disorder a diagnosis of erythromelalgia was entertained. The patient was begun on empiric therapy of one aspirin tablet per day. Remarkably, after 48 hours, his hand lesion had completely resolved.

The thrombocytosis and leukocytosis were treated with hydroxyurea, with some initial improvement in the counts. A sudden dense right hemiparesis with aphasia subsequently developed consistent with a left hemispheric stroke. A cerebral CAT scan confirmed an infarction of the left basal ganglia. The patient's condition rapidly deteriorated up to his death one week later.

DISCUSSION

Erythromelalgia affects the extremities with erythema, heat, and intense stabbing or burning pain. Symptoms



FIGURE 2. Erythromelalgia in the ulnar nerve distribution of the right hand.

often occur intermittently, and onset of attacks may be related to extremity warming, dependency, or exercise.

Primary erythromelalgia classically presents with symmetrical involvement of the feet more commonly than the hands. In primary erythromelalgia there is no clinical or laboratory evidence of an associated disease process.

Secondary erythromelalgia presents with similar symptoms but with asymmetrical extremity involvement and an underlying disease that may cause the syndrome. In the study by Smith and Allen,² secondary cases all occurred in patients over age 40 with the greatest distribution in the 60 to 69 age group. These cases are frequently associated with myeloproliferative disorders, especially polycythemia vera. Other associated conditions include hypertension, venous insufficiency, diabetes mellitus, systemic lupus erythematosus, peripheral vascular disease, and rheumatoid arthritis.² Recently there have been case reports of drug-induced erythromelalgia with pergolide,³ bromocriptine,⁴ and nifedipine.⁵

A variety of conditions may present with pain and redness of an extremity. The presence of bounding pulses immediately rules out vascular insufficiency. Other conditions to be ruled out include acute gout, acute rheumatoid arthritis, bacterial cellulitis, metatarsalgia, and peripheral neuropathy.

Thermography performed on patients with erythromelalgia has revealed differences of up to 9°C between affected areas and normal contralateral skin.⁶ The intensity of subjective pain correlates well with the skin temperatures. Thermograms will improve or normalize with successful treatment of the disorder.

The pathophysiology of erythromelalgia remains controversial. Skin biopsies of affected areas reveal inflammation of arterioles with sparing of venules, capillaries, and nerves.⁷ Arterioles are sometimes occluded by thrombi, thus accounting for the acrocyanosis or gangrene occasionally seen in this disorder.

Treatment of erythromelalgia can often yield satisfying results. Cooling

and elevation of the involved extremity is usually helpful. In secondary cases, successful treatment of the underlying disease will often provide resolution of erythromelalgia. Smith and Allen² first noted that relief of symptoms was obtained with a single 650-mg dose of aspirin. In the series by Babb et al,⁸ 70% of patients responded well to aspirin therapy. Since patients often dramatically respond to small doses of aspirin, some authors consider a positive response to aspirin as a diagnostic test for this entity.^{6,8,10} The response to aspirin is thought to be secondary to the irreversible inactivation of platelet-derived cyclooxygenase. Interestingly, other antiplatelet agents without cyclooxygenase activity (sulfinpyrazone, sodium salicylate, dipyridamole) have no effect on erythromelalgia.

Erythromelalgia continues to be a rare but interesting phenomenon. It must be considered in the differential diagnosis of a painful, reddened extremity. Recognition is important because effective treatment is available and the response can be gratifying to both patient and physician.

Acknowledgment. The authors thank Irene M. Billow for her secretarial assistance in preparing this article.

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The need for cooperative professional relationships in diagnosing and treating male sexual dysfunction

TO THE EDITOR: The apparent conflicting views expressed by Dr Adrian W. Zorngiotti¹ and Drs John F. O'Connor and Monica J. Salerno² cannot at present be reconciled without a cooperative professional relationship between specialists involved in diagnosing and treating male sexual dysfunction. The primary reason is that all clinicians see just a "limited time exposure" of the patient's dysfunction and we are further frequently limited by our expertise in just our particular field.

In attempting to diagnose and treat these patients we need time to sort out the operative factors and possible etiologies; time not just to perform diagnostic tests, but also to permit us to observe the patient. Furthermore, the patient and his sexual partner benefit by being interviewed and observed by at least one other health care professional after his initial contact with usually either a primary care physician or a urologist.

Today, many professionals in this field believe in the value of a multispecialty approach to this frequently multifaceted and multifactorial syndrome, and recognize the significant role played by mental health care professionals, ie, usually certified sex therapists or psychiatrists with professional expertise in male sexual dysfunction.

It is precisely because impotence is but a single symptom with numerous causes that the viewpoints of Drs Zorngiotti, O'Connor, and Salerno must be respected. At any one point in time in a particular patient the impotence may be due to one organic etiology, more than one organic etiology, one psychogenic etiology, more than one psychogenic etiology, or any combination of the preceding. To make matters more complex these general etiologic categories have specific etiologies therein that may vary with time.

As a result of these observations it should be more widely recognized that a multispecialty approach to diagnosis and treatment is the *ideal* that should be available to patients with impotence

and their partners, permitting "treatment on a cooperative basis" as Dr Zorngiotti states, when the etiologies in any one patient are both organic and psychogenic.

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Jane V. Williams, MD

TO THE EDITOR: I was both delighted and saddened by Dr Naomi Bluestone's portrayal of Dr Jane V. Williams in a recent issue of the *Journal*.¹ The delightful description accurately represented a dedicated, knowledgeable physician who was also an extremely elegant person.

Many of us who knew Dr Williams were amazed at the most precise picture drawn of her by Dr Bluestone. It was almost as if she could step off the pages and we would once more have Janie. The use of the word "will not" instead of "won't" was typical. Janie very seldom used contractions in her speech.

I could spend many words to describe the dedication of this physician to her profession and to her community. But how does one improve upon an already beautifully executed portrait? Also, I could mention that one quarter of an inch difference in the hemline of a dress was not tolerated.

The picture was so accurate that it further impressed upon me that I had lost a friend and dear colleague—and I was made sad.

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Supermarket medicine

TO THE EDITOR: An astute futurist re-

cently shared with me a rather gloomy picture of medical care in the 1990s and beyond. He was concerned with our inability to communicate clearly the costs of medical care. This, he felt, will hurt us considerably. It was his opinion that we have attempted to accommodate to the cost cutting frenzy which has seized the system. We have, however, neglected to point out that quality medical care does not come cheaply.

Discount medical care, without the so called frills, will become least-common-denominator care. Welcome to medicine by the numbers. Compassion and caring will be squeezed out and discarded as irrelevant. Talking to patients will become a luxury, best left to ancillary staff. To be very cost effective, the "Provider" will spend the least amount of time per "Consumer" and see the maximum number of "them" per hour. Will there be "Bargain Days" in which "they" will be seen for less? How about "two-fers," where the husband and wife will be seen for one fee?

For this type of performance to succeed, a different type of provider will have to be recruited and trained. The speedy technician will be the role model to be emulated. Patients will no longer speak fondly of their doctors but will talk about their technicians. The term "doctor" will become obsolete.

The same observer wondered when would we ever learn that to compromise with doing things right only leads to the destruction of what we are trying so desperately to save. The concept of quality care will give way to producing the largest number of services with the least amount of damage. Quality control, not quality assurance, will be the key words. There will also be a "Complaint Department" serviced primarily by computers with clerical backup who will conclude the dialogue with a cheery, "Have a good day."

Even as one recoils from this surrealistic picture painted by the futurist, there is a sense that it may well come to be. Is the dawn of the new age to be the end of medicine as we have known it?

One thing is very clear. Without the active support and participation of our patients we will have difficulty in convincing our legislators that we are doing

the right thing. We must educate our patients as to what will happen when federal and state mandates combine to limit the incomes of physicians so drastically that they opt to seek other alternatives. The frightening scenario is that once quality care is gone, it will take an awfully long time to repair the damage.

We owe it to our patients, our families, our successors, and ourselves not to let this happen.

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Penicillin treatment of syphilis in pregnancy

TO THE EDITOR: The New York State Department of Health has issued guidelines calling for penicillin treatment of syphilis in pregnancy.¹ These guidelines state, "pregnant women with a history of penicillin allergy should first be carefully questioned regarding the validity of the history. They should then be skin tested and either treated with penicillin or referred for desensitization."¹ These guidelines are identical with those issued by the Centers for Disease Control.² Those who are knowledgeable about penicillin will ac-

knowledge that penicillin allergy histories are often quite vague, sometimes because the reaction to penicillin occurred in childhood or because of uncertainty about the name of the drug to which someone had a reaction. Thus in numerous uncertain cases, penicillin hypersensitivity can only be evaluated by skin testing. At the present time, only one of the penicillin metabolic determinants is commercially available despite the fact that some of the unavailable minor determinants have been described now for over 20 years.³ It has been estimated that by not using a minor determinant preparation as many as 3-14% of cases of penicillin allergy will be missed by standard skin testing with benzyl penicilloyl-polylysine (major determinant) and aqueous penicillin.⁴ Thus the patient who has a history of penicillin allergy but is skin tested only to the major determinant and aqueous penicillin may still suffer an allergic reaction despite being skin test negative. The situation is further complicated by the fact that positive skin test reactions to penicillin determinants commonly occur in as many as 7% of patients without a history of penicillin allergy.⁵ Thus it is conceivable that individuals who have never had a penicillin reaction and claim a vague history of drug allergy (which they mistakenly may relate to penicillin) may

have a 7% incidence of positive penicillin determinant skin test positivity. These skin test positive individuals are supposed to be advised to undergo desensitization if they are pregnant. Desensitization is a labor intensive and potentially risky procedure which requires hospitalization and close physician monitoring. Thus although one can understand the need to treat both the mother and fetus effectively for syphilis, the policy of skin testing and desensitization in pregnant patients with syphilis has important implications and presents problems which should be carefully considered by health officials.

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The Medical Society of the State of New York is an approved provider by the New York State Department of Education to offer this training in identifying and reporting child abuse (required in New York State for license registration for all physicians, optometrists, psychologists, dental hygienists, and others).

For information about where you can attend a Medical Society sponsored course in your area, contact Cathy Falanga at (516) 488-6100, extension 317.

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Rabies update 1990

The beginning of the decade of the 1990s has witnessed a dramatic change for rabies in New York State. The mid-Atlantic raccoon rabies epizootic which entered New Jersey from Pennsylvania in the fall of 1989 entered New York State in two areas in the spring of 1990, Steuben County from central Pennsylvania and Sullivan County across the Delaware River from eastern Pennsylvania and New Jersey. Additionally, the re-emergence of fox rabies from Canada occurred this year on the Quebec border of Franklin County, the first case in the north country since early 1987.

In 1989, the confirmed cases of rabies were limited to 54 bats statewide. It was also the first year since 1940 that a terrestrial animal was not confirmed rabid in New York. Bat rabies continues to be a problem throughout the state but the incidence has remained constant over the last 20 years; that is, 2–5% of the bats submitted for rabies examination are confirmed rabid each year.

The Mid-Atlantic Epizootic

The mid-Atlantic raccoon rabies epizootic has been an interesting yet tragic tale of human manipulation of wildlife. Since the 1950s, raccoon rabies has been a problem limited to the southeastern portion of the United States. Between 1977 and 1981, over 3,500 raccoons were imported with legal permits into Virginia from Florida. The first rabid raccoon in the mid-Atlantic outbreak appeared in West Virginia in 1977 and three more were confirmed rabid in Virginia in 1978. Since then, about 9,000 raccoons as well as other wild and domestic animals have been found rabid (as of December 31, 1989) from Virginia, West Virginia, Maryland, Pennsylvania, Delaware, New Jersey and the District of Columbia. Raccoon rabies has now spread to New York State.

Between 1987 and the end of 1989, 2,925 raccoons were confirmed rabid in the states involved, demonstrating the immense impact the raccoon rabies outbreak has had in this part of the country. During this time, rabies cases in these states occurred in 188 foxes, 546 skunks, 39 ground-hogs, 19 horses, 46 cows, 176 cats, 22 dogs, and one or more cases in pigs, sheep, goats, rabbits, bobcats, and deer.

The first rabid raccoon in New York from the mid-Atlantic epizootic was diagnosed on May 4, 1990, in the town of Addison, Steuben County. It was 2½ months before the next case was reported in Steuben County. Sullivan County had a rabid raccoon confirmed on July 3 with

four more cases over the next few weeks. At the end of September, the raccoon epizootic intensified. Sullivan County had 23 rabid raccoons, 6 rabid skunks, and one rabid fox. Raccoon rabies now exists in four more counties: Chemung, Allegany, Cattaraugus, and Orange. The Steuben County cases are expected to remain sporadic before becoming established in the raccoon population. The situation along the Delaware River may become more dramatic since the raccoon populations in suburban areas are more dense than the populations found in farm country. The threat of raccoon rabies from either side of the river exists (for the counties of Sullivan, Orange, and Delaware) with the whole southern Hudson River Valley potentially threatened by a spread from New Jersey.

The importation of animals incubating the disease could also become a contributing factor in the spread of rabies. On June 16, a cat was found rabid on the upper east side of Manhattan. The cat had been brought to New York City from the owner's summer home in Pennsylvania.

Rabies in Northern New York State

The reintroduction of fox rabies into northern Franklin County has some interesting aspects. First, the spread came from Quebec rather than southern Ontario where fox rabies is epizootic. Furthermore, the cases were concentrated in two small townships on the Canadian border until late summer when cases appeared in adjoining townships. This probably reflected the movement of the young born in 1990 into new areas. There have been 29 foxes, seven skunks, and seven cows confirmed rabid during 1990 in Franklin County. The cattle cases have resulted in over 25 people being given postexposure rabies prophylaxis. It is expected that Franklin County will spend over \$15,000 on human rabies treatment this year.

Preventive Efforts

The rabies situation in New York State this year requires constant surveillance and public education. Thirty-one of the 62 counties in New York require rabies vaccination of dogs for licensure pursuant to Section 2145 of the Public Health Law. Eight of these 31 counties opted for this mandatory vaccination program when threatened by raccoon rabies. An additional five counties are now contemplating the program. Additionally, an emergency amendment to the New York State Sanitary Code was adopted on October 22, 1990, requiring compulsory cat vaccination against rabies in those counties where rabies has been confirmed in raccoons.

Physicians and other health care providers are advised to be aware of the rabies situation in their area. Since bats are considered rabid until proven negative, all bat bites should warrant immediate postexposure treatment unless the specimen can be delivered to the rabies laboratory for examination without delay.

Each decision concerning postexposure rabies treatment for any animal exposure rests with the patient and the attending physician. Consultation and information on submitting specimens is available from local

health units, the Bureau of Communicable Disease Control at (518) 474-3186, the Rabies Laboratory at (518) 869-4527 and, during off-duty hours, through the Department of Health Duty Officer at (518) 465-9720.

Child growth monitoring project

The New York State Department of Health's Bureau of Nutrition is conducting the Child Growth Monitoring Project to introduce standardized anthropometric measurements and growth assessment as an additional service provided to clients in the Women, Infants and Children (WIC) program. WIC is the leading nutrition intervention program in the United States, providing supplemental food and nutrition services to low-income women, infants, and children at nutritional risk.

The Child Growth Monitoring Project is a combined effort of the Bureau of Nutrition's Surveillance Program and the WIC Program. Beginning on August 15, 1990, approximately 100 WIC sites across New York State began regular growth monitoring for all infants and children enrolled in the program. WIC Program staff from these participating sites have been trained in the proper techniques for measuring weight and height, and anthropometric equipment has been carefully selected for the project according to its accuracy, ease of operation, and durability. It is expected that child growth monitoring will eventually become standard procedure for the more than 500 WIC Program sites in the state.

There is a strong relationship between growth, food and nutrient intake, and health. Measuring growth is a relatively simple, sensitive, and cost-effective method to assess the child's nutritional condition and overall health status. Body weight is the simplest measurement and is the most reliable indicator of growth in children. Height (or length of the body in the case of infants) is also a useful indicator of growth, especially among older children. For either measure, an accurate determination of the child's age is essential to ensure a correct interpretation. These measurements are then combined to form three indicators of health and nutritional status for comparison with reference populations. The indicators used are weight-for-age, height-for-age, and weight-for-height.

The goal of growth monitoring in nutrition and other public health programs is to promote child health, human development, and quality of life. Growth monitoring is not an intervention in itself, but rather a process or strategy that may be used to generate important actions for the client, the health professional, program managers, and policymakers.

The potential uses of growth monitoring in nutrition and other public health programs include the following:

- Source of data for screening and identifying high-risk children to target interventions and services;
- Tool for nutrition and health education;
- Strategy to motivate client participation and regular attendance at the WIC sites;
- Promotional tool to stimulate the interest and awareness among communities, government and

policymakers;

- Source of information for program monitoring and evaluation;
- Source of information for health planning and policy formation at the state and national level.

Thus, the success of growth monitoring in improving health and nutritional status ultimately depends on how effectively it is used to achieve some or all of these purposes. The positive impact on a child's health and nutritional status will be the result of improved screening, targeting and implementation, and delivery of services.

The data generated by the Child Growth Monitoring Project will be linked with the US Centers for Disease Control Pediatric Nutrition Surveillance System (PedNSS). The purpose of the PedNSS is to continuously monitor the status of the major nutrition problems among high-risk infants and children. This surveillance system is a vital source of information useful at the state and federal level for program evaluation, health planning, and policy formation.

Currently, over 40 states and territories participate in PedNSS which collects, analyzes, and reports program-based data including measurements of height, weight, birthweight, and hemoglobin and/or hematocrit. Comparisons are made with reference population data and the nutritional status of the surveillance population is characterized by the prevalence of short stature (low height-for-age), underweight (low weight-for-height), overweight (high weight-for-height), anemia (low hemoglobin and/or hematocrit), and low birthweight.

PedNSS data are analyzed by CDC and reports are returned to participating states monthly, quarterly, and annually for use in patient follow-up, program planning and management, and evaluation of health resource allocation at the state and local level. States also use PedNSS information to identify prevalent nutrition-related problems by age, ethnic group, and geographic area in order to target high-risk groups for intervention. At the federal level, PedNSS data from the participating states and territories are aggregated and reported for national health planning and policy formation.

The Bureau of Nutrition's Surveillance Program is also planning to match records for WIC Program prenatal women, infants, and children to the infant birth record. The linked records will contain invaluable information on prenatal characteristics, birth outcomes, and subsequent growth of the child. The surveillance database will be used to assess program coverage, target services, and evaluate program impact.

Population density and cancer mortality differential in New York State, 1978-1982

While previous investigations have reported differences in cancer mortality associated with urbanization gradients,¹⁻¹¹ conclusions from these studies have been limited since many of these reports relied upon an urban-rural

dichotomy^{4-6,11} or trichotomy⁸ as a crude measure of urbanization. Use of these limited categories potentially concealed important gradients in cancer mortality associated with increasing levels of urbanization. Further, these reports have generally relied on expansive areas, such as state or county, as the basic geographic unit of analysis. This makes it difficult to characterize the true level of urbanization due to the heterogeneous distribution of populations within these large areas.

A methodology developed by Nasca et al,¹² used minor civil divisions (eg, cities and towns) as the basic geographic unit of analysis in a study of cancer incidence and population density. This methodology was used to investigate patterns of cancer mortality in New York State, exclusive of New York City, between 1978 and 1982 using five population density groupings.

The population density for each community in New York State was determined using 1980 census data and information on total land area for each city, town, and villages. Villages located within towns were assigned to the population density of the town in which they were located. Communities were then rank ordered according to population density. This ranking was used to create population density quintiles, each containing an approximately equal number of people.

Standardized mortality ratios (SMRs) were calculated for both males and females within each population density quintile for all cancer deaths combined, and for selected site-specific cancer deaths among residents of New York State, exclusive of New York City, during 1978-1982. The precision of each SMR was assessed by calculating 95% confidence intervals.^{13,14} A t-test¹⁵ was used to determine if a significant linear relationship existed between population density and cause-specific SMRs.

A significant linear relationship was observed between increasing population density and increasing standardized mortality ratios for all cancer deaths combined among both males and females (Fig 1). Standardized mortality ratios in the two most urban population density quintiles were significantly higher than expected, while standardized mortality ratios were significantly lower than expected in the two most rural quintiles.

For site-specific cancer deaths, males demonstrated a significant linear relationship between increasing population density and deaths for cancer of the oral cavity and pharynx, esophagus, stomach, colon, gallbladder, pancreas, lung, prostate and kidney. Among females, a significant linear relationship was observed between increasing

population density and deaths due to cancers of the stomach, colon, liver, and breast. Deaths due to cancers of the rectum, malignant melanomas of the skin and cervix also exhibited unusual, but nonlinear, mortality patterns across population density groupings.

These data show a direct association between population density and mortality from all cancer deaths combined among both males and females. This observation is consistent with previous reports of increased cancer mortality in urban areas.^{4-6,8,9} In contrast, elevated cancer deaths, for both sexes combined have been observed in rural areas of Georgia.¹¹ Data of this type are most useful in generating hypotheses for further studies to define specific etiologic factors operating within population density groupings. Population density, as measured in this investigation, may represent a surrogate measure for other cancer risk factors, such as socioeconomic status, personal health behaviors, and differential exposures to environmental agents, which are related to cancer morbidity and cancer mortality. It is also possible that differences in cancer mortality across population density quintiles may result from an interaction of urban-rural differences in diagnosis, treatment, access to care and survival.

A complete description of this study may be found in *International Journal of Epidemiology* 1990, vol. 19, no. 3.

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Expansion of the AIDS drug assistance program (ADAP)

The New York State AIDS Drug Assistance Program (ADAP) recently expanded the list of prescription drugs

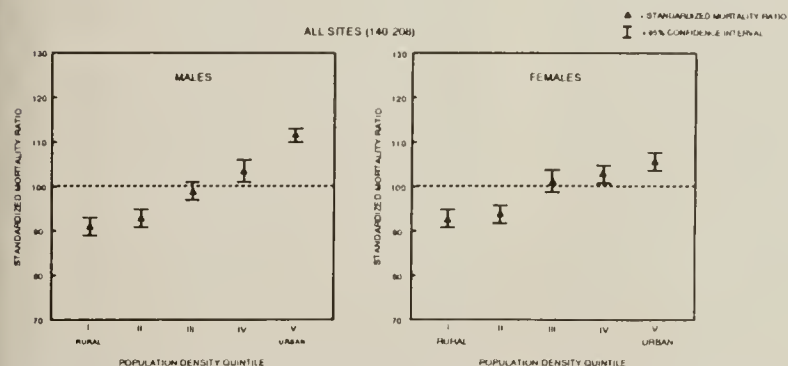


FIGURE 1. Standardized mortality ratios for cancer deaths, New York State, excluding New York City, 1978-1982.

available to clients through the program. ADAP is a federally funded program providing US Food and Drug Administration (FDA) approved drugs without cost to New York State residents seeking treatment for HIV infection or AIDS and who have inadequate or no insurance coverage, are not eligible for Medicaid, and meet medical eligibility criteria.

The ADAP program began in September 1987 to help ensure access to AZT (zidovudine or Retrovir) for all New Yorkers infected with HIV. In June 1989, the scope of the program was expanded to cover other FDA-approved drugs found effective in prolonging life through treatment or prevention of HIV-related illness. These included alpha interferon (indicated for treatment of Kaposi's sarcoma), along with three additional drugs (aerosolized pentamidine {Pentam 300, Nebupent}, trimethoprim-sulfamethoxazole {Bactrim, Septra}, and leucovorin) for pneumocystis carinii pneumonia (PCP) prophylaxis.

Recently, ADAP received a total of \$5.3 million from the federal government to provide additional drugs for treatment of PCP and other opportunistic infections. Among those approved for PCP prophylaxis were sulfadoxine pyrimethamine (Fansidar), trimethoprim and dapsone. Seven other drugs were added for use against common opportunistic infections. Acyclovir (Zovirax) and ganciclovir (Cytovene) are two antiviral agents now covered under the program. Additional medications available for fungal infections include clotrimazole (Mycelex), fluconazole (Diflucan), ketoconazole (Nizoral), nystatin, and acidulin. Table I presents indicated usage for each drug available through ADAP.

Approximately 5,400 individuals have been approved for participation in ADAP since it began in 1987. It is estimated that 50% of these individuals have no medical or prescription drug insurance coverage, 20% have only partial insurance coverage and 30% receive drugs through the program on an interim basis while awaiting New York State Medicaid eligibility determination and approval. The New York State Medicaid Program covers all FDA-approved and medically indicated prescription drugs for

TABLE I. Prescription Drugs Available through ADAP

Drug	Indication/ Opportunistic Infection	Date Available
Zidovudine (Retrovir)	HIV infection	September 1987
Pentamidine (Pentam 300, NebuPent)	Pneumocystis carinii pneumonia	June 1989
Trimethoprim-sulfamethoxazole (Bactrim, Septra)	Pneumocystis carinii pneumonia	June 1989
Leucovorin	Pneumocystis carinii pneumonia	June 1989
Dapsone	Pneumocystis carinii pneumonia	March 1990
Sulfadoxine/pyrimethamine (Fansidar)	Pneumocystis carinii pneumonia	March 1990
Trimethoprim	Pneumocystis carinii pneumonia	March 1990
Alpha interferon	Kaposi's sarcoma	June 1989
Acyclovir (Zovirax)	Herpes simplex	March 1990
Ganciclovir (Cytovene)	CMV retinitis	March 1990
Clotrimazole (Mycelex)	Candidiasis	March 1990
Nystatin	Candidiasis	March 1990
Fluconazole (Diflucan)	Candidiasis, Cryptococcal meningitis	March 1990
Ketoconazole (Nizoral) with acidulin (as needed)	Candidiasis, Coccidiomycosis, Histoplasmosis	March 1990

treatment of individuals infected with HIV.

A brochure entitled, "Free medication to help people with HIV or AIDS!" is available by contacting the New York State Department of Health AIDS Institute at the address below.

This brochure contains general information about the AIDS Drug Assistance Program, eligibility requirements, drugs covered by the program, and the ADAP hotline number. To order a copy of the brochure, contact: NYS Department of Health AIDS Institute, Corning Tower, Room 729, Empire State Plaza, Albany, NY 12237, (518) 474-3045.

**DSM-III-R TRAINING GUIDE FOR
DIAGNOSIS OF CHILDHOOD
DISORDERS**

By Judith L. Rapoport, MD, and Deborah R. Ismond, MA. 224 pp. New York, Brunner/Mazel Publishers, 1990. \$17.95 (paperback)

In June 1984, this *Journal* published a review of Judith Rapoport and Deborah R. Ismond's *DSM-III Training Guide for Diagnosis of Childhood Disorders*. Now, just seven years later, DSM-III is obsolete, replaced by DSM-III-R, and a new review of DSM-III-R is in order. This, to use a cliché, is both good news and bad news; good because it recognizes the ground swell of uneasiness among child psychiatrists concerning the lack of proven validity in the diagnostic categories of DSM-III, its confusion of symptoms with diagnosis, its athoretical nature; bad news because it also reflects our primitive knowledge of the etiology, familial patterns, natural history, and the diverse manifestations of psychiatric disorders in childhood. DSM-III-R shares all the good and bad of its predecessor, DSM-III. It is an improvement, however, attempting to clarify such criteria of DSM-III as were "unclear, inconsistent, or contradictory," and to reclassify "disorders that were out of line with scientific and clinical evidence."

Dr Rapoport and Ms Ismond recognize the shortcomings of our taxonomy but recognize also that diagnostic uniformity is essential for research and clinical communication. Their *DSM-III-R Training Guide* stresses the differences between criteria in DSM-III and in DSM-III-R; clarifies and comments on the criteria for the new classification and the new axis placement of psychiatric disorders of childhood and adolescence. A comparison between DSM-III and III-R childhood categories is conveniently summarized in a table. Among the major changes in III-R is the inclusion of attention-deficit hyperactivity disorders and conduct disorders under the heading of the disruptive behavior disorders. Attention-deficit-hyperactivity disorder replaces the old ADD with or without hyperactivity; the residual type of ADD is deleted. The conduct disorders are categorically simplified into group type, solitary aggressive type, and undifferentiated

type. An oppositional defiant disorder is added. The criteria for pervasive developmental disorder have been sharpened, and the subgroup of autism more clearly defined. PDD and mental retardation have now been placed on Axis II. Borderline intellectual functioning is now subsumed under a V code in Axis II. The diagnosis of reactive attachment disorder of infancy or early childhood suggests that interference with early bonding is a predisposing factor and that the age of onset can be up to the age of five years.

The training guide also attempts to find parallels between Axis I diagnosis for children and adolescents and Axis II personality disorders in late adolescence and in adults. Adult criteria for schizophrenia, for mood disorders, for anxiety disorders, and for organic mental syndromes are translated into criteria suitable for children and adolescents.

The delineation of and the changes in diagnoses, criteria, axis placement, deletions, and additions found in III-R are of course important in guiding the documentation of our daily clinical work. Equally important in this era of transition is the discussion provided by the III-R training guide as to *why* the changes were made, the pros and cons of the decisions, and the problems which still are unsolved for each. These discussions will help the younger clinician understand that the taxonomy and the criteria of III-R are not rigid and must be applied with sensitivity guided by experience.

In structure, the DSM-III-R training guide is similar to that of DSM-III. The book is divided into three sections and two appendices. Section I, "An overview of psychiatric diagnosis in pediatric age groups," includes a brief historical perspective on diagnosis, the problems of definition, the validity and reliability of DSM-III-R diagnoses for childhood disorders, and specific diagnostic issues in child psychiatry. Section II, "Basic concepts for pediatric psychiatric diagnosis," details the uses of the multi-axial diagnostic structure, the purpose of Axis II, and the use of Axis III, IV and V, and provides guidelines for a gross quantification of severity of psychosocial stressors (Axis IV) and for documentation of the highest level of adaptive functioning (Axis V). This section concludes with a warning that "diagnostic process is much broad-

er than recognizing DSM-III-R entities, involving an evaluation that must also consider management of the child, his family and possibly his environment."

Section III deals with "major classifications and differential diagnosis." Here many of the changes appearing in III-R are considered in detail (personality disorders, developmental abnormalities in the first five years of life, schizophrenia, mood disorders, the disruptive behavior disorders, anxiety disorders, eating and tic disorders, specific developmental disorder and other disorders) and described and illustrated. Use of V codes (condition not fitting criteria for mental disorder, yet serious enough to merit attention and treatment) is also described and illustrated. In this guide, just as in its predecessor, problems in the interpretation and application of the criteria, differential diagnosis, and case vignettes bring the criteria into the clinic and experience of us all. In the appendices, appendix I compares the DSM-III-R criteria with the classification in ICD-10. A useful table in this guide demonstrates similarities and differences between the two systems. What is of interest is the greater concordance between III-R and ICD-10 than between DSM-III and ICD-9. As more knowledge of etiology and pathogenesis of psychiatric disorders of children and adolescence is obtained, even greater overlap is to be expected. Appendix II concludes this volume with a brief table of characteristics and content of structured clinical interviews. The importance of such interviews, particularly in drug studies, is underlined.

This training guide is a well-balanced, clearly written presentation of the status of classification of childhood and adolescent psychiatric disorders as it stands in DSM-III-R. The literature cited may be too selective (the same two studies quoted in DSM-III finding more than 20% of children and adolescents seen at academic child psychiatry clinics fitting criteria for major depressive disorder are quoted in this guide) and the Rapoport-Ismond statement that "neurological evaluation has a selectively small role in the process of diagnosing childhood disorders" may arouse a markedly differing opinion. Nevertheless the training guide for DSM-III-R, just as that for DSM-III,

is a distinct contribution in translating the *Diagnostic and Statistical Manual* into serviceable language and use. We look forward to a training guide for DSM-IV!

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A DSM-III-R CASEBOOK OF TREATMENT SELECTION

By Samuel Perry, MD, Allen Frances, MD, John Clarkin, PhD. 395 pp. New York, Brunner/Mazel Publishers, 1990. \$42.50 (hardcover)

This book is about treatment planning in psychiatry and employs vignettes to illustrate the major diagnostic entities. Each vignette is followed by a practical discussion of treatment options, systematically organized in a format that deserves to be widely adopted. The authors demonstrate that the design of a treatment plan requires the integration of almost every aspect of the patient's personal and social circumstances. Diagnosis is but one of the elements to be considered.

With our apprenticeship approach to graduate medical education, it is only by endless discussion of cases that senior clinicians are able to transmit what they know. When the clinical setting does not provide sufficient variety, some important topics may never be explored. The heart of this book is the clinical wisdom conveyed by the analysis of 53 cases. If each psychiatry house officer would read this book (written in familiar hospital vernacular) at the beginning of training, he or she would have a quick overview of years of case discussions. This is not a cookbook but a model of how to analyze and use clinical data. For example, planning for one alcoholic patient calls for confrontation of denial, while for another sensitive avoidance of confrontation is prescribed.

The *Diagnostic Manual* is concerned with diagnosis of individuals, and it is oriented toward the needs of hospitals and institutions. Thus this book, which is oriented toward the *Manual*, does not portray all the activities of psychiatrists. Individual psychodynamic psychotherapy is emphasized. Family and group therapies are considered in every

case, and many ingenious reasons are presented for not using them. Family therapy is portrayed primarily as a strategy for obtaining information or for giving instruction. In one case, there is discussion of issues to be taken up if the husband and wife are treated conjointly, but no suggestion that referral be made to a specialist in this modality. Day hospital is mentioned, but one gets little sense of treatment planning for the chronically disabled who attend most day hospitals and public clinics.

As general hospital inpatient care has become increasingly oriented toward psychopharmacology and management, consideration of the meaning of behavior or symptoms is often crowded out of daily teaching. This book includes many plausible brief psychodynamic hypotheses that demonstrate the role of psychodynamic thinking about the severely ill.

Controversial therapeutic issues are for the most part thoroughly discussed, but in connection with prophylactic use of antiparkinsonism agents only the negative arguments are presented. A few treatment ideas are extreme; most are beautifully sensible. The authors could have highlighted some of their imaginative clinical tactics that are far from routine. One hopes that the reader will be able to emulate their flexibility in negotiating with patients and their practice of educating patients about the specific characteristics of the diseases that afflict them. Thus, in one vignette, participation of the narcissistic patient in development of his treatment plan included consideration of whether he would prefer an approach based on Kohut's formulations or Kernberg's. Another case illustrates how an effective treatment plan required organization to ensure participation of every resident in the program.

A few vignettes are by other authors. Those by Kraepelin and Freud remind us that clinical writing can be graceful. Cases by guest experts are more pedantic and, in some cases, so telegraphically condensed that important points are likely to slip by unnoticed.

In sum, this book does not attempt to teach the entire practice of psychiatry. It accomplishes its mission of making clear that the choice of treatment is based on more than the DSM-III-R diagnosis. It is an important step in the right direction. It should be very helpful for those who want to learn quickly and easily a lot about sophisticated inpatient and outpatient hospital psychiatry.

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HEALTH CARE IN THE PARISIAN COUNTRYSIDE, 1800-1914

By Evelyn Bernette Ackerman. 258 pp, illustrated. New Brunswick, NJ, Rutgers University Press, 1990. \$45.00 (hardcover)

This book concerns the management of disease among rural peasant families in the department of the Seine-et-Oise near Paris from the days of Napoleon to the First World War. In her analysis of the department, which was comparatively wealthy and literate, Ackerman challenges previous scholarship that depicts peasant thinking as isolated and constant. Ackerman, who is excellently schooled in historiography, provides the reader with a good perspective on contemporary scholarship while developing her own view of the patterns of popular belief and behaviors about sickness and the body which unfolded over the course of a century.

Ackerman recounts the types of cure sought by country people, including self-medication and the panoply of folk healers, remedy sellers, traveling cures, priest-doctors, midwives, and the more officially sanctioned doctors, surgeons, pharmacists, and *officers de sante*. The author discusses this community of sick and their healers in terms of power relationships, cultural assumptions, and the influence of external forces such as the national government, Jennerian vaccination, a departmental hygiene council, public health programs, and the bacteriological revolution. Throughout her analysis, she establishes an understanding between stability and change in the management of disease that breaks new ground alongside the writings of Michel Foucault, Jacques Donzelot, and the so-called Whiggish history of inevitability. The author, who writes of change without presuming the inevitability of progress, recounts how, and in what form, new ideas coexisted with the old; the context in which regulars and irregulars traveled the same roads and treated the same patients; the interplay between humors, miasmatic theory and bacteriology; and the ratiocinations that made for an easy affinity between the Hippocratic concept of the body and disease and the seemingly antithet-

ical goals of modern science. In effect, French peasants had a variety of options to choose from in their search for help with sickness or pain. Choice depended upon the seriousness of the disease, its endemic or epidemic nature, cost, the seductive language of cure, accessibility to healer, judgmental attitudes of medical professionals, the appeal of symbols in the drama of healing (puking, purging, bleeding, blistering, etc), and the character of peasant life itself. As the author explains, choice became more a process of addition than of replacement. New ideas and new categories of healers worked alongside more traditional ideas and healers.

Ackerman deftly recounts the external influences on the Seine-et-Oise residents. In particular, she notes the context of the state's increasing involvement from Napoleon's reorganizing the profession and popularizing smallpox vaccination, the Restoration's laissez-faire philosophy that minimized the role of the national government in health matters, the Second Empire's attempt at supervision of health and hygiene as a result of the cholera epidemics of 1832 and 1849, and the Third Republic's national campaigns against the degenerative influences of alcohol and tuberculosis, and rendering smallpox vaccination obligatory.

The interested reader will find a wealth of information and insight in this work. Change, according to Ackerman, did not come at the level of reasoned discourse but through a variety of sometimes paradoxical efforts that continued into the 1930s. This is a most welcome addition to the corpus of the social history of medicine.

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THE MANAGEMENT OF PAIN (VOLUME I & II)

Second Edition. Edited by John J. Bonica, MD. 2,195 pp, illustrated. Pennsylvania, Lea & Febiger, 1990. \$249.00 (hardcover)

Pain remains a formidable enemy of the physician. For the patient, pain drains physical and mental health by destroying sleep, impairing function, and producing depression and anxiety. Although much has been written about

the various aspects of pain, *The Management of Pain*, edited by John J. Bonica, MD, represents the first comprehensive textbook dealing with the basic and clinical sciences of pain and its associated disorders and syndromes.

Dr Bonica is a recognized international authority in pain management, having chaired the Department of Anesthesiology and directed the Multidisciplinary Pain Center at the University of Washington, Seattle, Washington. He is also the founder and Honorary President of the International Association for the Study of Pain. His collaborators in this herculean task include C. Richard Chapman, PhD, Professor of Anesthesiology, Psychiatry and Behavioral Sciences and Psychology; Wilbert E. Fordyce, PhD, Emeritus Professor of Rehabilitation Medicine; and John D. Loeser, MD, Professor of Neurological Surgery, all of the University of Washington. The work includes an additional 95 contributors from many fields in the basic and clinical sciences, particularly anesthesiology, psychiatry and behavioral medicine, nursing, pharmacology, physiology, oncology, neurosurgery, orthopedic surgery, ophthalmology, otolaryngology, oral surgery, physical therapy, rehabilitation, and occupational medicine.

Like the first edition of the textbook produced in 1953, the intent of the authors is to create a complete "encyclopedia" reference work for practitioners from every specialty. Four years in the making, the effort spans 100 chapters, five parts, 21 sections, two volumes, and 2,120 pages, with a weight of 13 lbs, 4 oz. The cost of the entire work is \$249.00. The division between Volumes I and II marks a pragmatic midway point in the presentation of the material and is not due to philosophical thematic differences. Part I consists of basic and clinical sciences, specifically a historical overview; definition and taxonomy of pain; anatomy, physiology, and biochemistry of pain mechanisms; epidemiology; psychology; and the general introduction to pain management through interdisciplinary/multidisciplinary pain programs for patient care, education, training, and research.

Acute painful disorders and chronic pain syndromes involving different parts of the body are discussed in Part II. There are two special chapters dealing with these entities in infants, children, and the elderly. A fine feature of Part II is that it creates a general reference framework for the specific regional pains presented in Part IV.

Part III deals with the various approach methods used to evaluate patients with complex pain syndromes. An integrated approach is stressed due to the time-consuming and comprehensive nature of such assessments.

Pain of anatomic specific body areas (eg, head, neck, chest, abdomen, pelvis, back, and extremities) is presented in Part IV. A general overview summarizes the section's relevant anatomy, physiology, evaluation, etiology, and differential diagnosis. The practical nature of this classification system is complementary to Part II and has been adopted by the International Association for the Study of Pain as axes I and II of its classification system.

The various therapies for the management of pain are discussed in Part V. The specific modalities used to control the symptoms of acute and chronic pain are organized in descending order of frequency, utility, and invasiveness. The indications, contraindications, complications, side effects, technique, and relevant basic science are described for each procedure. Many of the basic interventions (eg, TENS, drugs, simple regional blocks, and certain psychological and physical therapies) are presented in sufficient detail for either the primary care physician or subspecialist consultant to understand and apply them. Pain control by complex anesthesia and neurosurgical methods completes the perspective by acquainting the reader with the entire panoply of available strategies. Overall the presentation is balanced in order to optimize that combination of modalities for achieving the best results in the patient with a complex pain syndrome.

The text is amply illustrated by consistent, two-tone, black and white drawings. A major effort has been made to minimize redundancy by developing general overview and introductory chapters. A certain amount of repetition occurs in the discussion of various aspects of specific pain syndromes and the results of therapeutic modalities. According to the authors, the purpose of the duplication is to emphasize key points and minimize the need for flipping back and forth through sections. Each chapter includes important references from primary and secondary sources. There are no appendices in the text. Lastly, smaller type is used throughout the text for material that has academic merit but marginal practical utility.

Similar texts in the field include R. P. Raj (ed), *Practical Management*

of Pain, Yearbook Medical Publishers, 1986 (\$148.00); S. Anderson et al (eds), *Chronic Non-Cancer Pain: Assessment and Practical Management*, Kluwer Academics, 1987 (\$22.99); G. M. Aronoff (ed), *Evaluation and Treatment of Chronic Pain*, Urban and Schwartz, 1985 (\$68.00); G. D. Burrows et al (eds), *Handbook of Chronic Pain Management*, Elsevier, 1987 (\$53.50); J. L. Echtertnach (ed), *Pain*, Churchill, 1987 (\$35.00); and R. Mann (ed), *The Management of Pain*, Parthenon, 1988 (\$45.00).

While each has advantages in terms of practicality, cost, size, etc, none is as comprehensive as this "bible of pain." The second edition of *The Management of Pain* has preserved the first edition's clarity of vision and evenness of format and quality. These are remarkable accomplishments when one considers that the first edition was essentially under the sole authorship of Dr Bonica whereas the second edition includes 95 contributors and an exponential explosion of basic science and clinical material.

There are several areas of concern. The cost of the textbook is prohibitive for many practicing physicians. Rather, it will serve as a resource in medical libraries and clinics handling patients with pain. Continued advances in pain research and management will date the text's material in five to ten years. Lastly, despite several chapters dealing with the inter- and multidisciplinary team approach to pain, the role of the primary care physician is left unclear. The authors recognize that education in all areas on pain is essential and that the lack of a designated team physician results in fragmented care.

Nonetheless, the effort of Dr Bonica and his colleagues has indeed been monumental; the exposition is catholic and thorough. This textbook will be "the" reference on pain and is recommended to all individuals who are regularly involved in the care of patients with pain.

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ADVANCES IN PAIN RESEARCH AND THERAPY: MYOFASCIAL AND FIBROMYALGIA

Volume 17. Edited by James R. Friction, DDS, and Essam A. Awad, MD. 376 pp, illustrated. New York, Raven Press, 1990. \$105.00 (hardcover)

The resurgence of interest in muscle pain syndromes in the past decade has led to an abundance of symposia and continuing medical education (CME) courses on the subject. Most of these have focused on either myofascial pain or fibromyalgia. Those of us not firmly entrenched in either camp are left wondering what features of fibromyalgia sufficiently distinguish it from myofascial pain to warrant a separate label, and vice versa. The goal of this book is "to provide clinicians and researchers with the most current body of knowledge of both myofascial pain and fibromyalgia." For the first time experts from both camps appear in the same volume, allowing the reader to compare and contrast the clinical and basic science aspects of these important muscle pain syndromes.

The editors were the organizers of the First International Symposium on Myofascial Pain and Fibromyalgia, held in May 1989 in Minneapolis. The book is a compilation of 22 papers presented at the meeting and includes contributions from 34 authors from six different countries, representing four medical specialties and dentistry. Included are contributions from some of the most respected names in the field of muscle pain: Travell, Bennett, Wolfe, Simons, Moldofsky, and Henriksson to name a few.

The first two chapters are overviews of muscle pain syndromes, one written by a leading authority in myofascial pain (David Simons) and the second by a leading authority in fibromyalgia (Robert Bennett). Each provides an excellent review from his own unique perspective, and they conclude with a discussion of the relationship between fibromyalgia and myofascial pain. Although both conclude that these syndromes are two distinct conditions, the reader gets a sense that the authors are not as convinced as they once were.

The next two chapters review recent research into central and peripheral nervous system mechanisms of muscular pain. Mense's discussion of his work on peripheral nociception is well written and concise. The discussion of central mechanisms of muscle pain by Sessle gets bogged down in recitations of neuroanatomy. The major take home message is summarized in the final four pages, which I suggest reading first.

The clinical features and epidemiology of myofascial pain and fibromyalgia are covered in the next four chapters. Wolfe contributes an excellent chapter, outlining the many sources of bias in

studies of muscle pain syndromes, and concludes with some suggestions for improving future research in this area.

Objective diagnostic techniques including the use of pressure algometers, sleep studies, strength testing, and biopsy, are described in parts of four separate chapters. Cutting edge techniques such as MRI spectroscopy are only touched on. Awad reviews in detail his own pioneering biopsy studies from almost 20 years ago and briefly summarizes more recent studies. Henriksson discusses muscular changes in fibromyalgia but only touches on the results of his research in support of the existence of a muscular "energy deficiency state." The balance of the chapter describes diagnostic tests that could be used to identify such areas of energy deficiency.

Other topics covered include the relationship of muscle pain to disability, masticatory muscle hyperactivity, psychosocial factors, and immune regulation. The final four chapters offer a spectrum of approaches to the management of muscle pain. Of note is the plea from Lewit that we pay attention to the important role motor dysfunction plays in the pathogenesis of these disorders.

Major complaints about the book include its redundancy (difficult but not impossible to avoid in the proceedings of a symposium), the variable quality of the contributions, the omission of the titles of papers in the references, and the high cost. Although most of the content is available from other sources, this book achieves its goal of bringing together in one volume experts in both fibromyalgia and myofascial pain. It is recommended reading for anyone who deals with this spectrum of muscle pain disorders.

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THE MYTH OF HETEROSEXUAL AIDS: HOW A TRAGEDY HAS BEEN DISTORTED BY THE MEDIA AND PARTISAN POLITICS

By Michael Fumento. 411 pp. New York, Basic Books, Inc, Publishers, 1990. \$22.95 (hardcover)

Since the publication of this book in late 1989, much has been written about the conclusions and assumptions presented in it. As the author states, the question he is most frequently asked is, "Whatever got you interested in

AIDS?" Mr Fumento is a political writer with an academic background in political science and law. There is a sense from the introduction that as a political writer he became increasingly concerned that the public policy implications of the AIDS epidemic are based on inappropriate conclusions of epidemiologic studies. In particular, Mr Fumento has been most concerned that the evidence supporting widespread infection of HIV in heterosexuals in the United States is misplaced, and indeed such an epidemic will not occur. While not denying the presence of cases of heterosexual transmission, the author goes on to attempt to debunk the concept that such an epidemic in the United States is imminent. An essential theme running throughout this book is the minimalization of the chance of this occurring.

In this regard, we cannot ignore the evidence from the developing world, especially Central Africa. Fumento attempts to deal with this in a chapter entitled "But What about Africa?" In this chapter he identifies a number of practices which he states can account for a substantial number of HIV-infected Africans. These include inadequate screening of blood for HIV, rates of homosexuality and bisexuality which are greater than those previously reported, and the lack of circumcision. While all may play a role in the well-documented rapid spread of HIV infection on the continent, multiple investigations confirm the role of heterosexual transmis-

sion in Africa, perhaps enhanced by other sexually transmitted diseases. In this case, Africa does provide an important reference point for the developed world. We are seeing a dramatic increase in the incidence of other sexually transmitted diseases (STDs) in the inner cities of our country and there is certainly significant preliminary data which appear to imply that an increase of HIV infection is following these other STDs. While this may not now be a significant issue for higher socioeconomic groups, it clearly does have significant implications for our policy makers.

Perhaps most important, we need to understand the circumstances which give rise to books such as these. The use of almost any data available in the public domain to support a given view is not uncommon in the popular press, and Mr Fumento uses such information with license. As with any statistics, epidemiologic data can be twisted to reach whatever conclusion an author wishes to reach, particularly in the non-peer-reviewed setting of popular publishing. To a great degree, the lack of precision of our earlier projections and assumptions is also coming home to roost. But whose fault is this? In the mid-1980s, when many of the higher projections of transmission and case load were being made, the environment was far different.

Both the media and relevant governmental authorities were asking epidemiologists and other scientists to provide them with information to make

important public policy decisions. With HIV epidemiology in its infancy, some projections were clearly inaccurate. This led to the headlines, articles, and government pronouncements which fill this book ("Now no one is safe from AIDS. It's a matter of settle down or die"). Nonetheless, as a result of a more mature epidemiologic effort and a clearer understanding of the natural history of HIV disease, we are now able to place many risks in their proper perspective. The risk of heterosexual AIDS is not the evanescent risk implied in this book, nor are all heterosexuals at risk. As with all behavioral risk-associated disease, the true risk is dependent on an individual's activities.

This book is a product of the supercharged political atmosphere surrounding the disease. As such, it contributes little to the constructive debate necessary to determine how to direct resources to the treatment and prevention of this disease. What the publication of this book does suggest is that further definitive studies need to be done to determine as precisely as possible the risk to heterosexuals. This is the last major epidemiologic question raised by HIV disease. These studies must proceed in a calm, unhurried, but well-defined manner in order to place the true risk of acquiring HIV heterosexually in perspective.

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OBITUARY LISTINGS

Nighat Ashraf, MD, Lowville. Died September 24, 1990; age 35. Dr Ashraf was a 1980 graduate of People's Medical College, Nawabshah, Pakistan. He was a member of the Medical Society of the County of Lewis, and the Medical Society of the State of New York.

Afaq Husain Barlas, MD, Staten Island. Died October 25, 1990; age 57. Dr Barlas was a 1956 graduate of the Dow Medical College, Karachi University, Karachi. He was a member of the American Geriatrics Society, the Richmond County Medical Society, and the Medical Society of the State of New York.

Leland Sylvan Berger, MD, Plattsburgh. Died July 1, 1990; age 52. Dr Berger was a 1964 graduate of Yale University School of Medicine. He was a Diplomate of the American Board of Radiology. His memberships included the Radiological Society of North America, Inc, the Medical Society of the County of Clinton, and the Medical Society of the State of New York.

George Bialkin, MD, Teaneck, NJ. Died October 12, 1990; age 84. Dr Bialkin was a 1933 graduate of the National University of Ireland. He was a Fellow of the American Academy of Pediatrics and the American College of Angiology and a Diplomate of the American Board of Pediatrics. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Emmanuel William Billard, MD, Bronx. Died September 23, 1990; age 92. Dr Billard was a 1922 graduate of Tufts University School of Medicine, Boston. He was a Fellow of the American College of Chest Physicians. He was a member of the American Thoracic Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

Daniel Joseph Bradley, MD, Amityville. Died November 11, 1990; age 84. Dr Bradley was a 1932 graduate of Cornell University Medical College. He was a Fellow of the American Academy of Family Physicians. He was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

James Joseph Burnett, MD, Binghamton. Died October 19, 1990; age 77. Dr Burnett was a 1941 graduate of the Hahnemann University School of Medicine, Philadelphia. He was a Fellow of the American College of Surgeons. He was a member of the New York Academy of Medicine, the Broome County Medical Society, and the Medical Society of the State of New York.

Ludwig J. Cibelli, Sr, MD, Garden City. Died November 26, 1990; age 83. Dr Cibelli was a 1934 graduate of New York Medical College, Valhalla. He was a Fellow of the American College of Obstetricians and Gynecologists and a Qualified Fellow of the International College of Surgeons. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Crispin Cooke, MD, Huntington. Died October 22, 1990; age 81. Dr Cooke was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. He was a member of the New York Academy of Medicine, the Medical Society of the County of Suffolk, and the Medical Society of the State of New York.

James Joseph Cotter, MD, Jamaica. Died August 5, 1990; age 70. Dr Cotter was a 1945 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the American Occupational Medical Association, Medical Society of the County of Queens, and the Medical Society of the State of New York.

Louis E. Daily, MD, Norwich. Died October 13, 1990; age 78. Dr Daily was a 1937 graduate of the University of Maryland School of Medicine, Baltimore. He was a member of the Medical Society of the County of Chenango and the Medical Society of the State of New York.

Carl Edward Day, MD, Buffalo. Died November 5, 1990; age 58. Dr Day was a 1957 graduate of Loyola University of Chicago Stritch School of Medicine, Maywood, Illinois. He was a Diplomate of the American Board of Surgery and

a Fellow of the American College of Surgeons. His memberships included the New York State Surgical Society, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Joseph DePietro, MD, Beechhurst. Died October 13, 1990; age 93. Dr DePietro was a 1920 graduate of New York University School of Medicine. He was a Fellow of the American College of Obstetricians and Gynecologists, a Qualified Fellow of the International College of Surgeons, a Fellow of the American College of Surgeons, and a Diplomate of the American Board of Obstetrics and Gynecology. His memberships included the New York Academy of Medicine, the American Occupational Medical Association, the New York County Medical Society, and the Medical Society of the State of New York.

William Dock, MD, Paris, France. Died October 17, 1990; age 92. Dr Dock was a 1923 graduate of Rush Medical College of Rush University, Chicago. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Clarence J. H. Durshordwe, MD, Buffalo. Died September 24, 1990; age 94. Dr Durshordwe was a 1923 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Fellow of the American College of Anesthesiologists and a Diplomate of the American Board of Anesthesiology. His memberships included the New York State Society of Anesthesiologists, the New York Academy of Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Edward Francis Falsey, MD, Brooklyn. Died November 3, 1990; age 80. Dr Falsey was a 1935 graduate of Yale University School of Medicine. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychiatric Association, the Association for the Advancement of Psychotherapy, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Dorothy Fisher, MD, Staten Island. Died September 27, 1990; age 73. Dr Fisher was a 1940 graduate of the Virginia Commonwealth University, Medical College of Virginia, School of Medicine, Richmond. She was a Diplomate of the American Board of Dermatology, Inc. Her memberships included the New York Academy of Medicine, the New York State Dermatological Society, the American Academy of Dermatology, and the Medical Society of the State of New York.

Leonard Joseph Flanagan, MD, Binghamton. Died September 23, 1990; age 84. Dr Flanagan was a 1933 graduate of Boston University School of Medicine. He was a Fellow of the American College of Surgeons. He was a member of the Broome County Medical Society and the Medical Society of the State of New York.

Jerome Harold Flatow, MD, Syracuse. Died September 1, 1990; age 80. Dr Flatow was a 1935 graduate of the State University of New York Health Science Center at Syracuse, College of Medicine. He was a Diplomate of the American Board of Internal Medicine. His memberships included the New York Academy of Medicine, the Medical Society of the County of Onondaga, and the Medical Society of the State of New York.

Robert Anthony Flint, MD, New Hartford. Died September 25, 1990; age 47. Dr Flint was a 1972 graduate of Facoltà di Medicina e Chirurgia, Università di Bologna, Bologna, Italy. He was a member of the Medical Society of the County of Oneida and the Medical Society of the State of New York.

Ludwig L. Forchheimer, MD, New York. Died September 15, 1990; age 84. Dr Forchheimer was a 1931 graduate of the Medizinische Fakultät der Julius Maximilians Universität, Würzburg, Bayern, Germany. He was a Qualified Fellow of the International College of Surgeons. His memberships included the New York Society for Clinical Ophthalmology, the New York County Medical Society, and the Medical Society of the State of New York.

William George Ford, MD, Snyder. Died October 14, 1990; age 83. Dr Ford was a 1933 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. His memberships included the New York

Academy of Medicine, the New York State Society of Internal Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

William G. Garson, MD, Woodhaven. Died July 30, 1990; age 66. Dr Garson was a 1955 graduate of Faculté de Médecine, Université de Genève, Geneva, Switzerland. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Barnet Halperin, MD, Brooklyn. Died October 9, 1990; age 83. Dr Halperin was a 1931 graduate of New York Medical College. His memberships included the New York Cardiological Society, the New York American Geriatrics Society, the American Academy of Family Practice, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Clarence Clifton Hare, MD, Vero Beach, Florida. Died October 30, 1990; age 89. Dr Hare was a 1928 graduate of the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. He was a member of the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Mohammad Hedjazi, MD, Staten Island. Died October 19, 1990; age 62. Dr Hedjazi was a 1955 graduate of the University of Teheran, Pahlavi Medical School, Teheran, Iran. He was a Fellow of the American College of Obstetricians and Gynecologists, a Fellow of the American College of Surgeons, and a Diplomate of the American Board of Obstetrics and Gynecology. He was a member of the Richmond County Medical Society and the Medical Society of the State of New York.

Nathan Mitchell Jason, MD, West Palm Beach, Florida. Died October 9, 1990; age 69. Dr Jason was a 1951 graduate of the University of Rochester School of Medicine-Dentistry. He was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Urology. He was a member of the American Urological Association, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Henry Lax, MD, New York. Died September 17, 1990; age 96. Dr Lax was a

1918 graduate of the Semmelweis Orvostudományi Egyetem, Budapest, Hungary. He was a Fellow of the American College of Cardiology and of the American College of Angiology. His memberships included the New York Academy of Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

George Lewin, MD, New York. Died May 23, 1990; age 93. Dr Lewin was a 1923 graduate of Friedrich-Wilhelms Universität Medizinische Fakultät, Berlin, Germany. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Kurt Lippmann, MD, Wayne, NJ. Died September 30, 1990; age 91. Dr Lippmann was a 1924 graduate of the Medizinische Fakultät, Albert Ludwigs Universität, Freiburg im Breisgau, Baden-Württemberg, Germany. He was a Fellow of the American Board of Family Physicians. His memberships included the New York Cardiological Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

Andrew Henry Lorick, MD, New York. Died October 16, 1990; age 81. Dr Lorick was a 1936 graduate of Howard University College of Medicine, Washington, DC. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Gabriel Louis Magassy, MD, Chevy Chase, Maryland. Died September 8, 1990; age 90. Dr Magassy was a 1924 graduate of Semmelweis Orvostudományi Egyetem, Budapest, Hungary. His memberships included the American Psychiatric Association, the Academy of Psychosomatic Medicine, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Angelo Manocchio, MD, Brooklyn. Died July 24, 1990; age 77. Dr Manocchio was a 1937 graduate of New York Medical College, Valhalla. He was a Fellow of the American College of Angiology. His memberships included the American Academy of Family Physicians, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Harry Cyril McNamara, MD, Hurley. Died September 9, 1990; age 70. Dr McNamara was a 1947 graduate of the University of Vermont College of Medicine. He was a member of the Medical Society of the County of Ulster and the Medical Society of the State of New York.

David Iser Mirow, MD, Salt Lake City, Utah. Died May 19, 1990; age 92. Dr Mirow was a 1932 graduate of the Medical College of Wisconsin, Milwaukee. He was a member of the American Academy of Ophthalmology and Otolaryngology, the New York County Medical Society, and the Medical Society of the State of New York.

Rosa E. Prigosen, MD, Brooklyn. Died July 14, 1990; age 96. Dr Prigosen was a 1922 graduate of Johns Hopkins University School of Medicine, Baltimore. She was a Fellow of the Academy of Pediatrics and a Diplomate of the American Board of Pediatrics. Her memberships included the American Association for Cancer Research, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Laszlo Reich, MD, Mount Vernon. Died July 22, 1990; age 84. Dr Reich was a 1930 graduate of Facolta di Medicina e Chirurgia, Universita di Siena, Siena, Italy. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

William C. Schraft, MD, New Rochelle. Died August 30, 1990; age 69. Dr Schraft was a 1944 graduate of New York Medical College, Valhalla. He was a Diplomate of the American Board of Pathology and a Fellow of the American College of Pathologists. His memberships included the New York Academy of Medicine, the New York Pathological Society, the American Society of Clinical Pathologists, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Martin Schweitzer, MD, Roslyn Heights. Died October 16, 1990; age 83. Dr Schweitzer was a 1938 graduate of Medizinische Fakultät der Universität Wien, Wien, Germany. He was a member of the New York Cardiological Society, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

William H. Seery, MD, Flushing. Died June 12, 1990; age 73. Dr Seery was a 1944 graduate of Albany Medical College. He was a Diplomate of the American Board of Urology. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Thomas Cornell Seymour, MD, Ghent. Died October 26, 1990; age 75. Dr Seymour was a 1942 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Columbia and the Medical Society of the State of New York.

Norman Arthur Sharaga, MD, Brooklyn. Died April 1, 1990; age 52. Dr Sharaga was a 1963 graduate of the New York University School of Medicine. He was a Fellow of the American College of Angiology and a Diplomate of the American Board of Internal Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Frederick Sheer, MD, Cranbury, New Jersey. Died October 15, 1990; age 83. Dr Sheer was a 1931 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Surgeons and the American College of Obstetricians and Gynecologists, and a Qualified Fellow of the International College of Surgeons. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Paul J. Soley, MD, Seattle, Washington. Died October 6, 1990; age 89. Dr Soley was a 1927 graduate of Cornell University Medical College. He was a Diplomate of the American Board of Urology and a Fellow of the American College of Surgeons. His memberships included the American Urological Association, the Dutchess County Medical Society, and the Medical Society of the State of New York.

Vivian Allison Tenney, MD, Bridgewater, Virginia. Died September 10, 1990; age 77. Dr Tenney was a 1939 graduate of Cornell University Medical College. She was a member of the Academy of

Psychosomatic Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

John M. Touhey, MD, Endicott. Died October 25, 1990; age 90. Dr Touhey was a 1926 graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia. He was a Fellow of the American College of Surgeons. He was a member of the New York Academy of Medicine, the Broome County Medical Society, and the Medical Society of the State of New York.

Louis A. Trovato, MD, Buffalo. Died October 23, 1990; age 75. Dr Trovato was a 1943 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. His memberships included the New York Academy of Medicine, the American Occupational Medical Association, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Marvin Warman, MD, Bronx. Died October 6, 1990; age 61. Dr Warman was a 1954 graduate of the University of Health Science Chicago Medical School, North Chicago. He was a Fellow of the American Academy of Family Physicians and a Diplomate of the American Board of Family Practice. He was a member of the American Geriatrics Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

John R. Whittier, MD, Orient. Died October 4, 1990; age 71. Dr Whittier was a 1943 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychiatric Association, the American Academy of Neurology, the Nassau County Medical Society, and the Medical Society of the State of New York.

Max Wolf, MD, New York. Died August 25, 1990; age 98. Dr Wolf was a 1916 graduate of the Universität Wien, Medizinische Fakultät, Wien, Austria. His memberships included the New York State Dermatological Society, the American Academy of Dermatology, the Society for Investigative Dermatology, the New York County Medical Society, and the Medical Society of the State of New York.

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FOR MY PATIENTS

KEEP YOUR HEAD – WEAR A BICYCLE HELMET

Dear Patient,

The bicycle, while usually considered a toy, is one of the major causes of serious head injury--especially in children. Although it is impossible for a bicyclist to completely avoid accidents, the regular use of an approved bicycle helmet can significantly reduce the risk of serious head injury and death. This is not only true for children, but for adults as well.

THE FACTS:

In the U.S., bicycle accidents cause about 600,000 emergency room visits and 1300 deaths per year.

70-80% of bicycle related deaths result from head injury.

One-third of all victims of bicycle accidents treated in the emergency room have head injuries.

25% of significant brain injuries in children 14 years or younger are bicycle related.

The death rate from bicycle injuries in children exceeds the death rates from accidental poisonings, falls, firearm injuries, and many major illnesses.

Safety helmets reduce the risk of bicycle related head injury by 85%.

Less than 10% of the estimated 90 million bicyclists wear helmets.

WHO NEEDS HELMETS?

Everybody. Although about one-half of bicycle related deaths occur to children age 16 or younger, adult injuries and deaths are an increasing problem. With the current trend towards healthy lifestyles, more adults have begun riding regularly. Unfortunately, helmet usage has remained low.

ON BIKE PATHS TOO?

Yes. Although about 90% of fatal bicycle injuries involve cars, the majority of bicycle crashes occur from falling off bicycles due to poor road/path surfaces or mechanical failure, as well as collision with fixed objects like curbs or trees. Serious injuries can occur anywhere. In fact, most occur close to home.

WHAT'S THE LAW?

Due to the evidence that these helmets work, one county in Maryland recently passed a mandatory bicycle helmet law for all riders. Presently, New York and California have laws requiring bicycle passengers under age 5 to wear protective helmets. It is possible that other counties and states will also pass similar laws in the near future.

BUT WHAT ABOUT THE COST?!

Most approved bicycle helmets vary in price from about \$25 to \$50. Considering the price of a bicycle today, this is relatively inexpensive. If one also considers that the costs to care for a severely head-injured bicyclist average more than 4.5 million dollars, the price of a good helmet is minimal.

WHERE TO GET ONE.

Most stores that carry bicycles also have a selection of helmets and salespeople who are knowledgeable about choosing the right one. You

may also want to try contacting some local organizations to see if helmet loaner programs exist or can be started for adults and children in your community.

WHAT TO LOOK FOR.

Two independent organizations set the standards for bicycle helmets. Look for the ANSI (American National Standards Institute) or the Snell Memorial Foundation approval on the helmet. If one of these approvals cannot be found, do not purchase that helmet. The helmet should fit comfortably and should not move around on one's head when properly adjusted. DO NOT use a helmet that does not fit correctly or one that is designated for other sports--it will provide inadequate protection.

OTHER SAFETY TIPS...

- Drive in direction of traffic.
- Observe traffic safety laws.
- Use lighting and reflective gear on bicycles and reflective clothing to improve visibility to motorists.
- Whenever possible, use lanes and paths designated for bicycles.
- Use appropriate hand signals.

REMEMBER...

The best cure for traumatic brain injury is prevention.

Both CHILDREN and ADULTS can benefit from the use of helmets.

Helmets must be USED, not just purchased, to be effective.



Committee on Accident and Injury Prevention
Prepared by Mark A. Mittler



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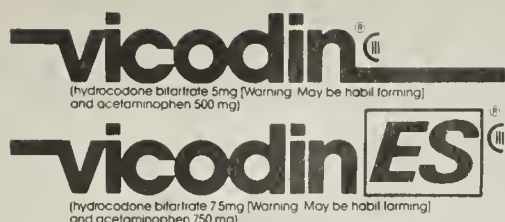
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daytime, nighttime, weekends.**

** (hydrocodone bitartrate 5 mg [Warning: May be habit forming] and acetaminophen 500 mg)

1. Data on file, Knoll Pharmaceuticals

2. Standard industry new prescription audit.

Please see adjacent page for brief summary of prescribing information.



INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.

WARNINGS:

Allergic-Type Reactions: VICODIN/VICODIN ES Tablets contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS:

Special Risk Patients: VICODIN/VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when VICODIN/VICODIN ES Tablets are used postoperatively and in patients with pulmonary disease.

Drug Interactions: Patients receiving other narcotic analgesics, antipsychotics, anxiolytic agents, or other CNS depressants (including alcohol) concomitantly with VICODIN/VICODIN ES Tablets may exhibit an additive CNS depression. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy:

Teratogenic Effects: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN/VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever.

Labor and Delivery: Administration of VICODIN/VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN/VICODIN ES Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence and mood changes.

Gastrointestinal System: The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN/VICODIN ES Tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

DRUG ABUSE AND DEPENDENCE:

VICODIN/VICODIN ES Tablets are subject to the Federal Controlled Substance Act (Schedule III). Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN/VICODIN ES Tablets should be prescribed and administered with caution.

OVERDOSAGE:

Acetaminophen Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Hydrocodone Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Revised June 1989

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(continued from p 14A)

CALIFORNIA

Mar 1-3. Advanced Seminars in Diagnostic Imaging. 18 Cat I Credits. Ritz-Carlton Resort Hotel, Laguna Niguel.

Mar 4-8. Magnetic Resonance Imaging. 27 1/4 Cat I Credits. Hotel del Coronado, San Diego. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077. Tel: (404) 641-9773.

Mar 10-15. 12th Annual Mammoth Mountain Emergency Medicine Ski Conference. Mammoth Lakes. Contact: Medical Conferences, Inc, PO Box 52-B, Newport Beach, CA 92662. Tel: (714) 650-4156.

Mar 16-18. Breast Imaging Update. 16 Cat I Credits. Fairmont Hotel, San Francisco. Contact: Radiology Postgraduate Education, Room C-324, University of California School of Medicine, San Francisco, CA 94143. Tel: (415) 476-5731.

Mar 21-23. Annual Aesthetic Surgery Symposium: Aesthetic Surgery of the Breast. San Francisco. Contact: Extended Programs in Medical Education, University of California, Room LS-105, San Francisco, CA 94143-0742. Tel: (415) 476-4251.

COLORADO

Mar 3-8. Magnetic Resonance Imaging: Update 1991—Winter Conference. 25 Cat I Credits. Marriott Hotel, Vail. Contact: Radiology Postgraduate Education, Room C-324, University of California School of Medicine, San Francisco, CA 94143. Tel: (415) 476-5731.

FLORIDA

Mar 11-13. 14th Annual Gold Coast Medicine Conference. 12 Cat I Credits. Good Samaritan Hospital, West Palm Beach. Contact: Laura J. Lehmann, CME Coordinator, Good Samaritan Health Systems, Inc, Flagler Dr at Palm Beach Lakes Blvd, West Palm Beach, FL 33402. Tel: (407) 655-5511.

VERMONT

Mar 6-8. Second Annual Primary Care Rheumatology Conference. Stratton Mountain Lodge. Contact: Sunnyview Rehabilitation Hospital, 1270 Belmont Ave, Schenectady, NY 12308. Tel: (518) 382-4500.

AROUND THE WORLD

FRANCE

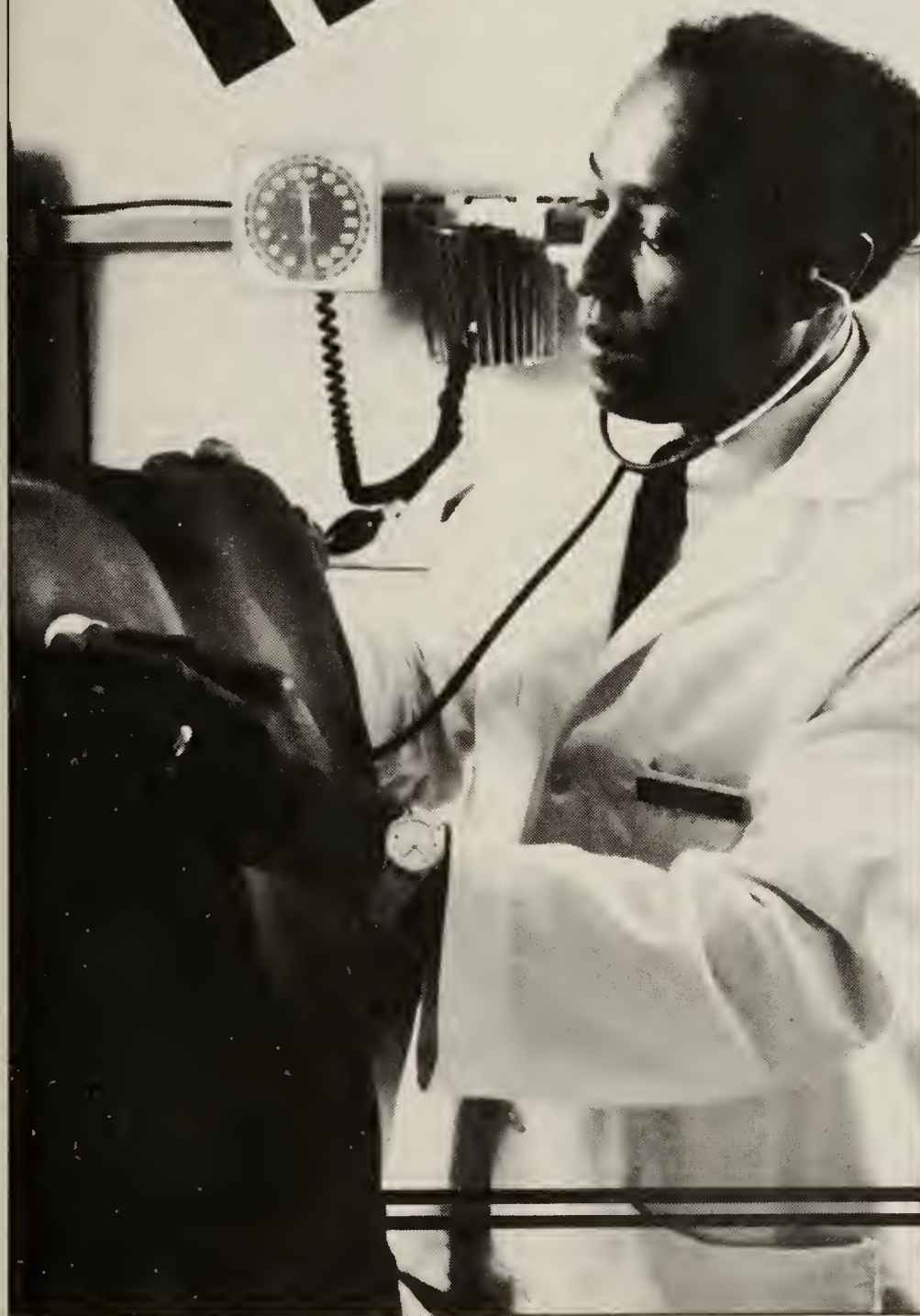
Mar 2-9. Ninth Winter Congress, Diagnostic Imaging. Val D'Isere, France. Contact: Winter Congress, Medical Seminars International, 18981 Ventura Blvd, Suite 303, Tarzana, CA 91311. Tel: (818) 700-9821.

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SAT., SUN., MARCH 23, 24, 1991. Neurology for Non-Neurologists. 13th Edition of Intensive Clinical Neurology Course (ICNC) by Lawrence P. Levitt, M.D. and Martin A. Samuels, M.D. 10 hours AMA Category I credit. For information contact Dr. Levitt, 1210 S. Cedar Crest Blvd., Allentown, PA 18103 (215) 776-8420.

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

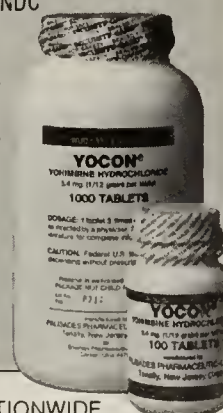
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Brief Summary.

Consult the package literature for prescribing information.
Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β -hemolytic streptococci).

Contraindication: Known allergy to cephalosporins.

Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of non-susceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:

- Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, serum-sickness-like reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055% to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
- Stevens-Johnson syndrome, toxic epidermal necrolysis,

and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.

- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonía, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

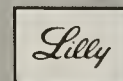
Abnormalities in laboratory results of uncertain etiology.

- Slight elevations in hepatic enzymes.
- Transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia.
- Rare reports of increased prothrombin time with or without clinical bleeding in patients receiving Ceclor and Coumadin concomitantly.
- Abnormal urinalysis; elevations in BUN or serum creatinine.
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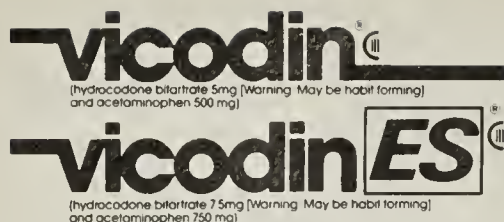
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1. Data on file, Knoll Pharmaceuticals

2. Standard Industry new prescription audit.

Please see adjacent page for brief summary of prescribing information.



INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.

WARNINGS:

Allergic-Type Reactions: VICODIN/VICODIN ES Tablets contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS:

Special Risk Patients: VICODIN/VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when VICODIN/VICODIN ES Tablets are used postoperatively and in patients with pulmonary disease.

Drug Interactions: Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with VICODIN/VICODIN ES Tablets may exhibit an additive CNS depression. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy:

Teratogenic Effects: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN/VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever.

Labor and Delivery: Administration of VICODIN/VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN/VICODIN ES Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence and mood changes.

Gastrointestinal System: The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN/VICODIN ES Tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

DRUG ABUSE AND DEPENDENCE:

VICODIN/VICODIN ES Tablets are subject to the Federal Controlled Substance Act (Schedule III). Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN/VICODIN ES Tablets should be prescribed and administered with caution.

OVERDOSAGE:

Acetaminophen Signs and Symptoms: In acute acetaminophen overdose, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Hydrocodone Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Revised June 1989

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APRIL 1991

AROUND THE STATE

EAST ELMHURST

Apr 5 or Apr 6. Emergency Medicine Oral Board Review Course. 7 Cat I Credits. LaGuardia Marriott Hotel. Contact: Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042. Tel: (718) 470-8650.

MANHATTAN

Apr 6. Radiosurgery/Electrosurgery in the Modern Medical Practice. Waldorf Astoria Hotel. Contact: Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear & Throat Hospital, 210 East 64th St, New York, NY 10021. Tel: (212) 838-9200, ext 2776.

Apr 8-13. Comprehensive Review of Physical Medicine and Rehabilitation.
Apr 18-19. First International Conference on Self-Destructing (Non-Reusable) Syringes. April 25-27. **Advances in Dermatology.** 17³/₄ Cat I Credits. NYU Medical Center. Contact: NYU Medical Center, Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

Apr 12-13. Controversies in the Management of Breast Cancer. Waldorf-Astoria. Contact: Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042. Tel: (718) 470-8650.

Apr 18-20. Fourth World Congress on Cancers of the Skin. New York City. Contact: Memorial Sloan-Kettering Cancer Center, Continuing Medical Education Office, Box 31, 1275 York Ave, New York, NY 10021. Tel: (212) 639-6754.

Apr 19. International Conference on Neuropathic and Musculoskeletal Pain. Sheraton Centre Hotel & Towers. Contact: Harry Hansen Management, Inc, 170 Old Country Rd, Suite 509, Mineola, NY 11501. Tel: (516) 739-2510.

Apr 27. 63rd Annual Scientific Session. 5 Cat I Credits. The Pierre Hotel. Contact: The New York Cardiological Society, Inc, 681 Lexington Ave, Suite 310, New York, NY 10022. Tel: (212) 888-5595.

MANHASSET

Apr 10. Physicians as Parent Educators in the 1990s. North Shore University Hospital. Contact: Department of Health Education/Community Affairs, North Shore University Hospital, 300 Community Dr, Manhasset, NY 11030. Tel: (516) 562-3045.

MELVILLE

Apr 17. Cardiology Update 1990—Interventions in Ischemic Heart Disease. Huntington Hilton. Contact: American

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COMMENTARIES

Tuberculosis transmission among health care workers

Over the past year, we have become aware of several episodes of tuberculosis (TB) transmission within hospitals and clinics throughout New York State (NYS). Such incidents include transmission of infection from one patient to another, as verified by epidemiologic, drug sensitivity, and phage typing analysis, and increased rates of tuberculin skin test conversions among hospital employees, including medical, nursing, technical, and housekeeping staffs. Why is such nosocomial spread of TB occurring throughout New York, and what must be done to control it?

One reason for the spread is that there are more cases of tuberculosis. In 1989, 3,202 cases, more than in any year since 1975, were reported in New York State. Reported cases of TB increased in seven of the last ten years in New York City (NYC), an increase of more than 68% from the all-time low reached in 1987.¹ New York State now has the highest tuberculosis case rate of any state in the nation, with almost 18 new active cases per 100,000 population each year; New York City alone accounts for approximately 10% of all TB cases reported in the United States.² This increase in morbidity leads to increased risk of exposure for health care workers.

The rise in the incidence of TB has not occurred uniformly throughout New York, but has been confined to certain population groups of the city and state. TB is concentrated in people from those neighborhoods or cities that remain overwhelmed by the traditional measures of deprivation, such as poor housing, poor nutrition, unemployment, and alcoholism, and that are under siege from the new problems of drug addiction and human immunodeficiency virus (HIV) infection.²⁻⁵ Much of the increase in TB is occurring in people infected with HIV, and possibly in their close contacts. Co-infection with HIV is probably the greatest risk factor for developing TB disease in persons previously infected with TB.^{6,7} Other groups at especially high risk for developing active TB include elderly New Yorkers residing within nursing homes, recent non-US born immigrants to New York, and prisoners in local and state correctional facilities.⁸⁻¹⁰ All these populations increased dramatically in the 1980s. As these social factors affecting TB morbidity are likely to remain during

the 1990s, exposure of workers caring for members of these groups will continue for the foreseeable future.

The lack of adequate, routine health care in the very populations at risk suggests that people will present at health care sites with TB in a more advanced stage. Some treatments for complications of HIV infection, such as aerosolized pentamidine, have been suspected of increasing the infectiousness of people with active pulmonary TB, as does bronchoscopy and induction of sputum.^{11,12} Exposure to people with infectious TB can occur in almost any health care setting, emergency room, hospital based or free-standing clinic, or nursing home, or during home-health visits.

Many of these factors have existed in the past. The mechanism of TB transmission—aerosolization of the tubercle bacillus by an infectious patient, usually during a cough—has been well understood for many years. When the TB sanatoria were closed in the 1960s and TB care was “mainstreamed,” protection of health care workers was accomplished by a high degree of diagnostic suspicion; early, vigorous therapy; and strict adherence to respiratory isolation procedures and the physical and organizational actions needed to stop transmission.

Today, knowledge of and vigilance against nosocomial TB infection has waned. The perceived “conquest” of TB in the earlier decades of this century led to a de-emphasis on TB in clinical training, and has produced a generation of health care workers untutored in TB and either unaware or unafraid of its personal consequences. Health care and public health administrators have often emphasized other services, at the expense of TB control. For instance, isolation of patients suspected of infection with TB is often given a lower priority than for other, perhaps less infectious illnesses. When TB patients are isolated, the responsibility for enforcement of such isolation is unclear. Isolation rooms in hospitals, when inspected, lack the negative air pressure, with venting to the outside, required to make TB isolation meaningful.

Hospitals and other health care facilities must develop rapid, efficient mechanisms of case detection in patients. Detection, of course, begins with an index of diagnostic suspicion consistent with the current increased level of dis-

ease. Once a case is detected, an effective program of staff protection from infection should be in place. Protection of staff includes prevention of microbial contamination of the air through early chemotherapy of the suspect case; training the patient to cover the nose and mouth while coughing; and masking of patients if they are removed from the room for any reason. Effective treatment of TB remains the crucial element in preventing transmission of disease to other individuals. However, backup preventive measures include effective ventilation and/or the use of ultraviolet lighting. Such measures should be used where suspected TB transmitters might contaminate the air; eg, emergency room, admitting areas, outpatient waiting rooms, x-ray units, bronchoscopy suites, and intensive care units.

Any lapses in such protection must be routinely followed by tuberculin skin testing, clinical assessment, and preventive therapy as needed. A system of control requires close coordination of efforts between the hospital administrative, nursing, and medical staffs, including infection control and employee health units. One key element, often overlooked, is improved communication within the institution so that individuals who may have come in contact with an infectious patient are aware of that fact and that those responsible for controlling TB are cognizant of all TB patients under care.

Skin testing after exposure is only meaningful if a baseline TB skin test has been done, documented, and is available for comparison. To ensure such availability, as well as screening for employee disease, Article 28 of the New York State Public Health Law requires pre-employment skin testing of all persons working in a hospital or medical facility in New York, not just employees, but volunteers, physicians with admitting privileges, students, and any other workers. A further requirement is periodic retesting at a minimum of every two years. Due to increasing TB exposure, some hospitals have required more frequent retesting.

Suspect or proven cases of TB are reported directly to the local city or county health department in which the patient resides, and, if different, to the county of the provider of care. Early case reporting to the health department should result in prompt patient contact evaluation. Such reporting is also essential in maintaining continuity of TB care after the patient is discharged. Laboratories, either hospital based or independent, also have a responsibility to report any positive acid fast bacillus (AFB) smears or *Mycobacterium tuberculosis* cultures to the local health department.

A separate reporting responsibility relates to nosocomial spread of TB within an institution. Suspected or proven spread of TB infection within a medical facility is reported directly to the New York State Department of Health's Office of Health Systems Management. Many hospitals ensure compliance with these various responsibilities by having the infection control team compile and report all reportable communicable disease. However, it is the ultimate responsibility of the attending physician to make sure that a particular TB case is reported promptly. It is also the responsibility of the hospital administrator to en-

sure that nosocomial infections are reported.

So what can be done to stop tuberculosis transmission among health care workers in New York State? One immediate action administrators of health facilities should take is a reevaluation of their preemployment and periodic retesting programs, assuring they are functioning well, and assessing the need for annual rather than biannual testing. TB control procedures should be reviewed with all staff. Rooms used for TB isolation should be assessed as to their suitability, ie, do they really provide negative pressure and venting out of doors? Finally, current reporting procedures should be reviewed and, if necessary, updated.

The federal government has announced a plan to eliminate tuberculosis by the year 2010.¹³ Such elimination can only occur if TB is controlled in New York State. Hospitals and other health related facilities, as part of this elimination plan, must become rededicated to preventing nosocomial transmission of TB in their institutions, using the time tested methods of TB control. A recent Centers for Disease Control report provides specific guidelines for preventing TB transmission within health care settings.¹⁴ The New York State, New York City, as well as local health departments are ready to assist in any way possible.

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14. Centers for Disease Control: Guidelines for preventing the transmission of tuberculosis in health-care settings, with special focus on HIV-related issues. *MMWR* 1990; 39:1-29.

Interstitial cystitis

Godec et al¹ in this issue of the *Journal* present a case illustrating the difficulties in diagnosing interstitial cystitis (IC). This poorly understood syndrome, with its florid symptom complex and the psychological ramifications described by the authors, is known to afflict at least 45,000 American women and is estimated to occur in perhaps five to ten times as many individuals.^{2,3} As the authors clearly point out, irritative voiding symptoms in the face of negative cultures warrant urological evaluation. Unfortunately, IC can rarely be diagnosed without cystoscopic examination under anesthesia,⁴ thus explaining why many cases are often overlooked even by urologists. Both major components of the symptom complex—around-the-clock urinary frequency and pelvic or suprapubic pain—are not invariably present,^{4,5} a point which also might explain the frequent misdiagnoses and inappropriate treatments (as illustrated in the presented case) which take place. The authors correctly point out that while an unequivocal diagnosis may be difficult or impossible to establish, the symptom complex, cystoscopic findings, and the absence of other diseases that can cause similar symptoms (eg, infections, bladder tumors, urinary calculi, etc) should suggest the possibility of IC.⁶

As difficult as it is to diagnose this condition, insights into its etiology remain even more elusive. While, historically, attention has been focused on infections, and neuropathic, vascular/lymphatic obstructive, inflammatory/auto-immune, allergic, endocrinologic, and psychogenic mechanisms,⁶ most investigators currently favor some sort of functional breakdown in the urothelial barrier permitting normal (and perhaps abnormal) urinary solutes access to the deeper layers of the bladder wall.⁷⁻⁹ It has been theorized that this may be due to a deficiency or abnormality in the protective mucopolysaccharide (glycosaminoglycan (GAG)) layer, although evidence to support this in humans currently remains entirely circumstantial.^{10,11} Whatever the mechanism, substances normally present in the urine do manage to enter a subepithelial location in IC bladders.^{7,9} The substances themselves may be toxic or may initiate irritative/inflammatory pathways eventually resulting in the vasodilation, edema, and focal chronic inflammatory infiltrates which characterize this condition histologically.¹² An additional area of research has focused on the role of mast cells which may be found in increased numbers in the detrusor layer in these patients.^{12,13} Unfortunately, identification of mast cells can be difficult. Furthermore, there is considerable variation in their quantities when serial biopsies from the same IC patient (who has not had a change in her clinical course) are examined,¹⁴ and they have equal abundances in the bladder walls of IC patients and pathological controls.⁴ It is likely that more than one cause for this condition exists, thus explaining the variable responses to treatments.

Numerous conservative regimens are quite effective in reducing symptoms, often for very long periods.¹⁵ The most popular of these include intravesical instillations of dimethylsulfoxide (DMSO),¹⁶ oxychlorosine sodium (Clorpactin WCS90),^{5,17} or silver nitrate, or oral administration of amitriptyline,¹⁸ or sodium pentosanpolysulfate (Elmiron).¹⁹ Sodium pentosanpolysulfate is believed to replenish the (possibly) deficient GAG layer;¹⁹ the mechanisms of action of the other remedies are unknown. Currently, clinical parameters are incapable of predicting which patient will respond favorably to any individual treatment; however, no more than 10% of all patients with IC will ever need to undergo major surgery for this condition.¹⁵ The vast majority of those who eventually require such treatment for symptomatic control will be "cured" by urinary diversion with or without cystectomy.⁶

In managing patients with IC, candor concerning this disease's uncertain etiology and prognosis must be offered immediately after it is diagnosed. However, favorable considerations—especially that there is no evidence that it presents a serious threat to health, that the disease rarely progresses,²⁰ and that all but approximately 10% of patients will eventually achieve considerable relief with endoscopic and/or pharmacologic therapy¹⁵—must be emphasized. In this way, patients can become partners in their own management—always a benefit in the treatment of chronic conditions with uncertain outcomes and responses to treatment.

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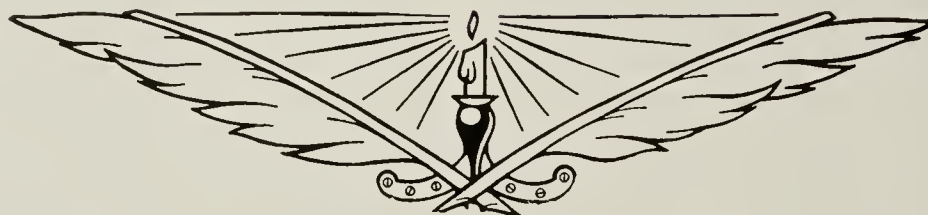
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Seroepidemiology and clinical aspects of human T-cell lymphotropic virus type I/II infection in a cohort of intravenous drug users in New York City

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ABSTRACT. To define further the magnitude, epidemiology, and clinical features of human T-cell lymphotropic/leukemia virus type I/II (HTLV-I/II) infection in 454 intravenous drug users in New York City, we evaluated previously frozen aliquots of sera for HTLV-I/II antibodies using enzyme-linked immunoassay, Western blot, and radioimmunoprecipitation techniques. We found HTLV-I/II infection in 18.9% of the subjects. Age ($p = 0.001$), race ($p = 0.001$), having a same gender sexual relationship ($p = 0.01$), and HIV-1 infection ($p = 0.041$) were clear correlates of HTLV-I/II infection. HTLV-I/II seropositive subjects, in contrast to seronegative subjects, had lower leukocyte counts ($p = 0.05$) and higher globulin ($p = 0.005$) and gamma globulin ($p = 0.009$) levels even when HIV-1 serostatus was controlled. The considerable prevalence of HTLV-I/II infection and the morbidity of HTLV-I/II-associated disorders strongly suggest a continued need to define the dimensions of HTLV-I/II infection.

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The prominence of the acquired immunodeficiency syndrome (AIDS) has stimulated interest about the public health significance of retroviruses other than the human immunodeficiency virus type I (HIV-I). Human T-cell lymphotropic virus type I (HTLV-I) was first identified in association with adult T-cell leukemia/lymphoma.¹⁻² Subsequently, investigators have uncovered associations between HTLV-I infection and tropical spastic paraparesis (TSP).³ There is also a recognized association between hairy cell leukemia and HTLV-II infection. Fortunately, these disease entities are rare. Nonetheless, questions remain about the magnitude of HTLV-I infection outside endemic areas of Japan, Africa, and the Caribbean basin.

While there have been many HTLV-I serologic investigations in the United States,^{4,5} few have combined HTLV-I seroprevalence with behavioral and clinical information. This is important for areas where HIV-I infec-

tion is prevalent. Limited information also exists about the prevalence of co-infection with transforming members of the human retrovirus family such as HTLV-I/II and cytopathic members such as HIV-I.⁶⁻⁸

Finally, the clinical significance of HIV-1 and HTLV-I co-infection is also incompletely understood. For example, does HTLV-I/II infection enhance or retard HIV-1 disease progression? In the midst of the current HIV epidemic, the significance of the answer to this question is critical. In this report, we present epidemiologic and limited clinical information in association with HTLV-I/II infection in a population of intravenous (IV) drug users enrolled in drug treatment programs.

PATIENTS AND METHODS

Study Population. During the period June 1, 1985, to September 1, 1985, we enrolled 454 patients in an HIV-1 seroprevalence study. These patients represented persons scheduled for admission or annual physical examination in selected methadone maintenance clinics in the boroughs of Brooklyn and Manhattan in New York City. At least one year of opiate dependence and an age of 18 years were eligibility requirements for enrollment in these clinics. Following a protocol approved by the Institutional (human subject) Review Board, pre-study information, counseling, and informed consent, each patient voluntarily agreed to participate in this study.

The study subjects' ages ranged from 19 to 62 years, with a mean age of 35 ± 0.35 years. Forty-nine percent of the population was black, 42% Hispanic, and 9% white; 70% were male and 30% female. Other characteristics of the study population have been previously described.⁹ The study sample did not differ in any significant manner (based on demographic and behavioral features) from the total 2,100 patients enrolled in these methadone maintenance clinics at the time of patient enrollment. Specifically trained interviewers administered a standardized questionnaire about demographic and socioeconomic status, drug use patterns, and sexual behaviors. Medical staff performed medical histories, physical examinations, and phlebotomy.

Assays. Frozen (at -20°C) aliquots of serum were thawed and evaluated for antibody to HTLV-I/II by an enzyme-linked immunoassay (Abbott, Abbott Park, Ill), as previously described.^{10,11} Specimens found initially reactive were retested. We subjected repeatedly reactive samples to confirmatory testing, which included Western blot followed by radioimmunoprecipitation assay (RIPA). A sample was determined to be positive for antibody to HTLV-I/II by RIPA if it precipitated at least two of the three major HTLV-I/II antigens. Recent data indicated that this methodology, used in intravenous drug users, detected anti-

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body to HTLV-I and HTLV-II, a closely related but distinct retrovirus.¹² We therefore considered a confirmed positive result as indicative of antibody to HTLV-I or HTLV-II (HTLV-I/II). This agrees with recommendations from the Centers for Disease Control.¹³ We assessed HIV-1 antibody presence using an enzyme-linked immunosorbent assay (ELISA) (Genetic Systems, Seattle, Wash), with confirmation of repeatedly positive ELISA specimens by Western blot (Dupont, Wilmington, Del). Sera with p24 and gp41 protein bands were considered positive.

Analysis. With the SPSS/PC+ statistical package, we used univariate measures (chi-square and Student t-tests) to analyze collected data. All significant associations were then subjected to stepwise logistic regression, using both a forward and, separately, a backward model.

RESULTS

We found serologic evidence for HTLV-I/II infection in 18.9% of the 454 subjects. Table I displays demographic data in association with HTLV-I/II infection rates. Only the associations between

TABLE I. HTLV-I/II Seroprevalence and Demographic Characteristics in Intravenous Drug Users in New York City, 1985

Characteristics	Number Tested	Sero-positive No.	%	Odds Ratio (95% Confidence Interval)
Sex				
Male	318	57	18	1
Female	136	29	21	1.0 (0.6-1.6)
Race				
White/other	39	3	8 [†]	1
Hispanic	193	25	13	1.8 (0.5-6.2)
Black	222	58	26	4.2 (1.3-14.3)
Age (yr)				
<30	130	11	8 [†]	1
31-35	157	26	16	2.1 (1.0-4.5)
36-40	88	21	23	3.4 (1.5-2.0)
>40	79	28	35	5.9 (2.8-12.8)
Marital status				
Married	173	28	16	1
Single	180	34	19	1.2 (0.7-2.1)
Divorced/separated/widowed	101	24	24	1.6 (0.9-3.0)
Educational level				
Some college	53	9	17	1
High school grad	109	21	19	1.2 (0.5-2.8)
Some high school	230	37	16	0.9 (0.4-2.1)
<8th grade	62	19	31	2.2 (0.9-5.3)
Borough of residence				
Manhattan	245	41	17	1
Brooklyn	209	45	21	1.4 (0.9-2.2)
Living status*				
With spouse and/or child	179	26	15	1
With parent	61	13	21	1.6 (0.8-3.3)
With self	98	23	23	1.8 (1.0-3.4)
Other	98	24	24	1.9 (1.0-3.6)
Source of income*				
Legitimate income	100	12	12	1
Public assistance	209	40	19	1.7 (0.9-3.5)
Illegitimate income	131	27	21	1.9 (0.9-4.0)
Employment status*				
Employed	100	13	13	1
Unemployed	332	66	20	1.7 (0.9-3.2)

* Missing information on some subjects.

[†] $p = 0.001$.

HTLV-I/II serostatus and race/ethnic group or age reached statistical significance. The mean ages of HTLV-I/II seropositive and seronegative subjects were 37.9 ± 0.4 years (95% confidence interval = 36.4-39.5) and 33.9 ± 0.8 years (95% confidence interval = 33.1-34.6), respectively. Significant differences in the mean ages of HTLV-I/II infected and non-infected subjects remained after adjusting for race/ethnic group.

The HTLV-I/II seroinfection distribution did not differ significantly by age of initiation or level of consumption of alcohol or tobacco. Additional behavioral information is available in Table II. All subjects admitted the use of intravenous drugs, and 92% admitted polydrug use. Seropositive and seronegative subjects were enrolled in drug treatment for a mean cumulative period of 32.1 ± 3.9 months (95% confidence interval = 24.3-39.3) and 21.4 ± 1.5 months (95% confidence interval = 18.5-24.3), respectively ($p=0.023$). When we controlled for age, differences in duration of drug use or of drug treatment enrollment between HTLV-I/II infected and non-infected subjects did not remain significant. Among males, a same gender sexual relationship in the last five years was significantly associated with HTLV-I/II infection. We did not observe this association among female subjects.

The prevalence of HTLV-I/II infection was not associated with the medical histories reported by this population (Table III). HTLV-I/II serostatus did not significantly vary (data not shown) in association with constitutional complaints of fever, diarrhea, night sweats, weight loss, anorexia, or malaise/lethargy. We did not in-

TABLE II. HTLV-I/II Seroprevalence and Behavioral Characteristics in Intravenous Drug Users in New York City, 1985

Characteristics	Number Tested	Sero-positive No.	%	Odds Ratio (95% Confidence Interval)
Intravenous route of administration most often used				
No	63	8	13	1
Yes	391	78	20	1.7 (0.8-3.7)
Drugs used				
Heroin only	20	2	10	1
Heroin and cocaine only	133	28	21	2.4 (0.5-11.0)
Heroin, cocaine, other	286	54	19	2.1 (0.5-9.3)
Other	14	2	14	1.5 (0.2-12.1)
Duration of drug use				
Less than 6 yr	98	5	5 [†]	1
Greater than or equal to 6 yr	356	81	23	5.5 (2.2-13.9)
Duration of drug treatment enrollment				
Less than 1 year	195	30	15	1
Greater than or equal to 1 year	259	56	22	1.5 (0.9-2.5)
Same gender sexual relationship in last five years				
No	399	68	17 [†]	1
Yes	55	18	33	2.4 (1.3-4.4)
Currently sexually active*				
No	40	5	12	1
Yes	411	78	19	1.6 (0.6-4.3)
Number of current steady sex partners*				
≥ 2	83	15	18	1
<2	369	70	19	1.1 (0.6-2.0)

* Missing information on some subjects.

[†] $p < 0.05$.

TABLE III. HTLV-I/II Seroprevalence and Clinical Features in Intravenous Drug Users in New York City, 1985

Clinical Features Medical History of:	Number Tested	Sero- positive		Odds Ratio (95% Confidence Interval)
		No.	%	
Tuberculosis				
No	421	76	18	1
Yes	33	10	30	3.7 (1.7-8.1)
Hepatitis				
Yes	119	19	16	1
No	335	67	20	1.3 (0.8-2.3)
Endocarditis				
Yes	18	2	11	1
No	436	84	19	1.9 (0.4-8.5)
Herpes simplex				
Yes	14	2	14	1
No	440	84	19	1.4 (0.3-6.4)

clude a history of genital ulcers at the time of the study. Physical findings did not significantly differ between HTLV-I/II infected and non-infected subjects.

HTLV-I/II seropositive subjects had lower mean levels of total white blood cell counts. Non-HTLV-I/II infected subjects exhibited a higher percentage of neutrophils and eosinophils and a lower percentage of lymphocytes and monocytes. In HTLV-I/II positive subjects, mean serum levels of alanine aminotransferase, lactic dehydrogenase, and albumin were lower. In contrast, the levels of aspartate aminotransferase were higher in the seropositive population. We found significant differences between seropositive and seronegative subjects in total white blood cell counts ($p = 0.05$), proportion of eosinophils ($p = 0.006$), serum globulin level ($p = 0.005$), and percentage of gamma globulin ($p = 0.009$). At the time of study entry, information about serum calcium levels and peripheral blood descriptions were unavailable. Rates of serologically documented hepatitis B or syphilis infection (51.5% and 3.7%, respectively, among HTLV-I/II positive subjects) were not significantly different between HTLV-I/II seronegative and seropositive subjects.

Previously, we reported an HIV-1 infection rate of 60.6% in this population.⁹ Sixty-five percent of the study population exhibited serologic evidence of infection by either HIV-1 or HTLV-I/II, and 14.3% had combined HIV-1 and HTLV-I/II infection. We categorized 307 subjects, based on available clinical information, according to the Centers for Disease Control classification system for HIV-associated infections.¹⁴ No subject met the criteria for Group I categorization (Table IV). At the time of this investigation, the study design did not include subjects who had symptoms associated with acute HIV infection (the CDC Group I criteria). We added a Group 0 status (subjects without any clinical or serologic evidence of HIV-1 infection). The HTLV-I/II seropositive subjects did not differ from HTLV-I/II seronegative subjects in the proportions of subjects in various stages of HIV-1 disease.

We analyzed the significant associations, using a forward or backward method of stepwise logistic regression. In both methods, the order of significance, from greater to lesser, was as follows: age; HIV serostatus; race; and having a same gender sexual preference. For both the forward and backward models, the chi-square value was 48.5 (with four degrees of freedom and a model $p < 0.0001$.)

DISCUSSION

Endemic areas of HTLV-I infection include Africa, Japan, and the Caribbean.^{15,16} In the United States, HTLV-I infection rates range from 0.025% among blood donors to 0.38% among persons attending a sexually transmitted disease treatment clinic in Baltimore.^{5,17} In these populations, parenteral drug abusers had higher infection rates. Nearly 3% of intravenous drug users in Baltimore, 12.9% in Detroit, up to 30% in New Jersey, and 49% in New

TABLE IV. HTLV-I/II Seroprevalence by CDC HIV Classification of New York City Intravenous Drug Users, 1985*

CDC HIV Classification Stage	Number Tested	HTLV-I/II Seropositive		Odds Ratio (95% Confidence Interval)
		No.	%	
Group 0	76	10	13	1
Group II	171	42	25	2.1 (1.0-4.6)
Group III	23	5	22	1.8 (0.6-6.0)
Group IV	37	10	27	2.4 (0.9-6.5)

* Note: Study design did not allow for the determination of subjects who satisfy CDC Group I. Group 0 was added for subjects without any clinical or serologic evidence of HIV infection.

Orleans¹⁷⁻¹⁹ were HTLV-I seropositive. In sera collected from drug abusers during 1971-1972 in 43 states, the overall HTLV-I infection rate was 6.3%.²⁰ Reports of HTLV-I infection in New York City have ranged from 3% to 23%.²¹ The present study is consistent with these trends, with an HTLV-I/II seroinfection rate of 18.9%. We add information about Brooklyn, where the infection rate was nearly one and a half times higher than in Manhattan. From studies in the United States, age, race, and duration of parenteral drug use are associated with higher HTLV-I infection rates.^{4,7,8,19,20}

The greater prevalence of infection among blacks may represent infection originating from HTLV-I endemic areas of the Southeastern United States and/or the Caribbean. In the present study, black patients were four times more likely to have HTLV-I/II infection compared to white patients. Regrettably, neither the nationalities nor geographic origins of the black patients were collected at the time of patient enrollment. Evidence of familial clustering of HTLV-I serologic findings suggests intergenerational transmission.²² Unfortunately, the design of this study did not allow for an examination of familial transmission or any other mechanisms that may underlie the role of race/ethnicity.

Patients who used heroin and cocaine were twice as likely to be HTLV-I/II seropositive as individuals who admitted only to the use of heroin. The greater injection frequency of persons using cocaine in combination with heroin, or alone (due to cocaine's shorter duration of action), may explain this observation. Still, after adjusting for age, there was no pattern of drug abuse to distinguish the HTLV-I/II infected subjects from the non-infected drug users.

Having a same gender sexual relationship within the last five years was also a significant factor for HTLV-I/II infection; having multiple sex partners was not. This is somewhat surprising. HTLV-I/II infection has not been previously shown to occur at appreciable levels in men who have sex with men. On the other hand, some investigators have found heterosexual promiscuity to be important,⁵ while others have not.^{17,18} While intrafamilial HTLV-I infection supports sexual transmission, the efficacy of heterosexual transmission of HTLV-I/II remains undefined. Similarly, further studies of HTLV-I/II infection in gay men would be useful. This investigation also disclosed a higher infection rate among females. A gender factor in retroviral infection has been reported.^{6,23} Al-

though not significant in this study, the higher female infection rate may suggest an additive effect of sexual behaviors and parenteral drug use. More importantly, the considerable infection rate among women has public health implications for perinatal transmission.

Recent data by Lee et al¹² have raised an important issue about HTLV serosurveys. Because of the significant amino acid sequence homology between HTLV-I and HTLV-II, previous HTLV-I seroepidemiologic studies require reexamination and replication. Virus isolation and gene amplification (polymerase chain reaction, PCR) are the only techniques known to distinguish between HTLV-I and HTLV-II infection. Because we collected the sera in the present examination before PCR methodology was available, it was not possible to use this technique. Accordingly, we used non-PCR methodology recommended by the CDC¹³ to categorize sera testing positive as evidence of HTLV-I/II infection.

Determining true HTLV-I seroinfection is also difficult in the presence of immune complexes.²⁴ Given the significant prevalence of hypergammaglobulinemia among drug users in the present sample, this may serve as another limitation in the serologic assessments in this study.

While HTLV-I infection has been the target of many investigators, there is increasing interest about co-infection by two or more members of the retrovirus family.^{6-8,17-21} Reported rates of co-infection with HTLV-I and HIV-1 have varied from 0.85% in Staten Island, NY, to 18% in Queens, NY.⁶ The 14.3% rate of dual HIV-1 and HTLV-I/II infection in this study is consistent with these trends. More importantly, the question persists as to the impact of HTLV-I/II infection on HIV disease progression. Some have suggested protective effects of HTLV-I on HIV-associated CD4 cell loss.²¹ Other researchers have noted lower parameters of immune function,⁸ increased HIV-1 replication in T cells, and more rapid progression to AIDS in populations with HTLV-I and HIV-1 infection.^{25,26} In the present investigation, HTLV-I/II serostatus was not associated with the stage of HIV disease. Further prospective studies in co-infected populations might clarify this relationship.

The clinical implications of HTLV-I/II infection have also stimulated discussion. Although a comprehensive review is beyond the scope of this paper, a few points are worth noting. Our knowledge is incomplete about the mechanisms involved in the association between HTLV-I and adult T-cell leukemia/lymphoma and tropical spastic paraparesis, or the relationship between hairy cell leukemia and HTLV-II infection. Limited information is also available about the clinical picture of HTLV-I infection in the absence of these malignancies and neurologic disorders. In a population of healthy carriers, Yasuda et al²⁷ have reported normal white blood cell counts and differentials, and increases in serum immunoglobulins and in the Tac-positive and CD2 cells.²⁷ The hematologic picture and liver function tests in HTLV-I/II infected individuals were generally normal in the present study. However, there were important trends, which we report with caution. In the HTLV-I/II infected subjects, the leukocyte counts were significantly lower, with a greater percentage of lymphocytes and monocytes, but a lower percentage of neutrophils and eosinophils. This is in contrast to the asso-

ciation between HTLV infection and eosinophilia observed by others.²⁸ Consistent with the study by Yasuda et al,²⁷ serum globulin and gamma globulin levels were significantly elevated in HTLV-I infected persons in this study.

It might well be suggested that the laboratory findings in the current study population might represent the consequences of HIV-1 infection/disease. However, when HIV serostatus was systematically controlled to avoid the confounding issue of concomitant HIV infection, the differences remained in the laboratory parameters between HTLV-I/II seronegative and seropositive subjects.

Although the present investigation may suffer from shortcomings that accompany retrospective, cross-sectional studies, it provides important information. This study provides confirmation about the significant prevalence of HTLV-I/II infection in parenteral drug users in the Northeastern United States. This investigation also suggests the need for additional studies to obtain information about correlates of HTLV-I/II infection.

Given current capabilities in treating HTLV-I/II associated malignancies and neurologic syndromes and the persisting questions of the impact of HTLV-I/II infection on HIV progression, more information is essential to define further and monitor the magnitude of HTLV-I/II infection. Simultaneously, it is important to develop and evaluate therapeutic responses to HTLV-I/II associated disorders. The infrequency of these disorders outside endemic areas of HTLV-I/II infection may lull some into a false sense of security. If our experience with the HIV epidemic has taught us anything, it has surely underscored the fact that aggressive efforts are most useful while the HTLV-I/II "window of opportunity" is still available.

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Experience in managing 70 patients with ruptured abdominal aortic aneurysms

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ABSTRACT. Seventy cases of ruptured abdominal aortic aneurysms (RAAAs) repaired over a 14-year period from 1975 to 1989 were analyzed. Age, heart disease, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, or specific postoperative complications did not correlate with mortality. If the time interval from arrival at the hospital to skin incision (emergency room (ER) or operating room (OR)) was less than six hours, there was no correlation with survival. Mortality correlated significantly with admitting systolic blood pressure, blood pressure at the time of skin incision, a comparison of ER to OR time of less than or more than six hours, blood loss of less than compared to more than ten units, and time in the operating room of less than five hours compared to more than five hours. Both time in the operating room and blood loss correlated with technical problems. Prior to 1985, 11 general and vascular surgeons had repaired RAAAs with a mortality of 76%. Since 1985, six vascular surgeons repaired RAAAs with a significant decrease in mortality (54%).

Our data indicate that patients profoundly hypotensive on admission or at the time of incision are unlikely to survive regardless of other factors; patients with a systolic blood pressure greater than 100 mm Hg have the best chance of survival; a delay of up to six hours prior to surgery in patients with a systolic blood pressure greater than 100 mm Hg does not increase mortality; and a smaller number of surgeons

operating on RAAAs increases survival. Based on these observations, we recommend that patients with a suspected RAAA and a systolic blood pressure greater than 100 mm Hg be brought to centers with surgeons experienced in RAAAs or transferred to such facilities within six hours and that such centers designate specific surgeons with an interest in RAAAs to develop the expertise to handle these cases.

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Improvement in cardiac and pulmonary support, perioperative monitoring, fluid resuscitation, anesthesia, and improved technique increased survival dramatically for elective abdominal aortic aneurysm repair in the 1960s and 1970s. However, mortality rates for ruptured abdominal aortic aneurysms (RAAAs) continue to be high, ranging from 25% to 80%.¹⁻¹⁷ Even these mortality figures are a gross underestimate, as only 38-64% of all patients with RAAAs ever reach the hospital.¹

Due to the presumed urgency for operative intervention in these cases, a majority of patients in this country are taken to the operating room with little preoperative preparation, to be operated on by the most readily available surgeon, in whichever hospital they happen to find themselves. Who should operate on these patients (general surgeons versus vascular surgeons), where the operations should take place (community hospitals versus specialized centers),²⁻⁴ and when the surgery should take place (immediately or after some preoperative preparations),⁵ has been addressed with conflicting views. The purpose of this study is to review our experience with RAAAs over the

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last 14 years, and to analyze the preoperative, operative, and postoperative factors that correlate with mortality.

METHODS

The charts of all patients with RAAAs were retrospectively reviewed for a 14-year period from January 1975 to January 1989. The patients' medical records were analyzed according to age, length of stay, symptoms, physical findings, heart disease, chronic obstructive pulmonary disease, hypertension, diabetes, admitting systolic blood pressure, blood pressure at the time of incision, time elapsed from emergency room to operating room, blood loss, time spent inducing anesthesia, time spent in the operating room, and operative technique. Urinary output was not analyzed. Postoperative complications were analyzed and correlated with a fatal outcome.

A ruptured aneurysm was defined by the presence of either retroperitoneal or intraperitoneal blood at the time of exploration. Patients who underwent urgent surgery for symptomatic but unruptured abdominal aortic aneurysms were excluded from this study. All patients were explored by a standard transabdominal approach, and in no patient was the retroperitoneal approach used. Operative mortality was defined as in-hospital death any time prior to discharge.

Prior to 1985, for ten years, 11 different surgeons repaired the RAAAs. Since 1985, six surgeons repaired the RAAAs; however, one surgeon operated on most (20/28) of the cases during this four-year time interval.

The Pearson correlation coefficient was used to determine if each normally distributed variable correlated significantly with any other. The Student's t-test was used to compare the means of normally distributed, independent, continuous variables for patients who survived versus patients who died. The Fisher's exact test was used to compare normally distributed dichotomous variables in patients who survived versus patients who died.

RESULTS

The following preoperative factors did not correlate with mortality: age (Tables I, II), sex (Table I), and history of heart disease, chronic obstructive pulmonary disease, hypertension, diabetes, cerebral vascular accident, peptic ulcer disease, or carcinoma. Multisystem failure as a result of initial cardiovascular shock was the most common cause of death. The primary cause of death in four patients was pulmonary insufficiency in the postoperative period. One patient died of hepatic failure, most likely as a result of the hypotension sustained on admission. Two patients died as a result of colon ischemia.

Mortality correlated significantly ($p < 0.05$, Fisher's exact test) with admitting systolic blood pressure (Table I): 92% of patients (12/13) with an admitting blood pressure of less than 50 mm Hg died, 66% of patients (20/30) with a blood pressure of 50 to 100 mm Hg died, and 55% of patients (15/27) with an admitting systolic blood pressure of greater than 100 mm Hg died (Fig 1). Mortality correlated significantly with the blood pressure at the time of skin incision (Table I): 100% of patients (6/6) with a pressure of less than 50 mm Hg died, 80% (17/21) with a pressure of 50 to 100 mm Hg died, and 56% (24/43) with a pressure of greater than 100 mm Hg at the time of incision died (Fig 1).

The time interval from arrival at the hospital to the skin incision (ER to OR) was not significantly different between those who survived and those who died (Table I), and did not correlate with mortality ($p = 0.35$) if the time interval was less than six hours (Tables I, III). However, there was a significant correlation with mortality ($p < 0.05$, Fisher's exact test) if patients whose time from arrival to the hospital to skin incision was less than six hours are compared to patients with ER to OR times greater than six hours (Fig 1). If patients arrived in the operating room within six hours, 65% (39/60) died, whereas if they arrived in the operating room six hours or more after admission, 80% (8/10) died.

The time in the operating room for the surgical procedure did not correlate with mortality (Tables I, IV). However, there was a significant correlation with mortality ($p < 0.05$, Fisher's exact test) for

TABLE I. Clinical Data on Patients with Ruptured Abdominal Aortic Aneurysms

	Survivors (N = 23)	Nonsurvivors (N = 47)	Significance ($p =$)*
Age	82	82	NS†
Sex	20/3	42/5	NS
Time to emergency room (min)	312	266	NS
Time in operating room (min)	213	196	NS
Admitting blood pressure (mm Hg)	109	81	0.008
Lowest blood pressure (mm Hg)	90	58	0.008
Blood pressure in operating room (mm Hg)	132	96	0.001
Transfusion (units)	9.1	13.4	0.009

* Student t-test used on all variables except sex, which was compared using the Fisher's exact test.

† NS, not significant.

patients who were in the operating room for less than five hours (64%) (30/47) compared to patients who were in the operating room for more than five hours (74%; 17/23) (Fig 1). Time in the operating room also correlated significantly with technical and potentially avoidable problems such as inferior vena caval injury, renal vein injury, iliac vein injury, aortic injury, and inadequate proximal control. Blood loss, like time in the operating room, correlated significantly with mortality ($p < 0.05$, Student's t-test, Table I, Fig 1). For blood loss of less than ten units, the mortality was 61% (22/26). The mortality was 74% (25/34) if the blood loss was more than ten units (Fig 1). Blood loss, like time in the operating room, correlated with technical and potentially avoidable problems ($p < 0.05$, Fisher's exact test).

The overall mortality for the entire 14 years was 67% (47/70). For the ten-year period prior to 1985, 11 surgeons repaired ruptured abdominal aortic aneurysms with an overall mortality of 76% (32/44). Since 1985, six surgeons operated on ruptured abdominal aortic aneurysms; however, one surgeon performed a majority of these operations (20/28). During this period, the mortality decreased significantly to 54% (15/28) ($p < 0.05$, Fisher's exact test). Since the late 1970s, there has been a progressive liberalization of the use of invasive monitoring such as Swan-Ganz catheters and more aggressive management of cardiac function during RAAA repair. These factors, combined with technologic advances in the intensive care unit over the last ten years, may have introduced some bias when the results of these two time periods were compared.

DISCUSSION

Data from this study indicate that patients profoundly hypotensive on admission for an RAAA or at the time of incision (systolic pressure less than 50 mm Hg) were unlikely to survive regardless of other factors. Patients with a blood pressure on admission or at the time of incision of more than 100 mm Hg had the best possible chance for survival with a technically flawless procedure. Contrary to these findings, some authors have reported that blood pressure on admission does not correlate with mortality.^{6,7}

TABLE II. Age as Related to Mortality

Age (yrs)	Mortality
0-59	42% (3/7)
60-69	81% (22/27)
70-79	74% (17/23)
>79	38% (5/31)

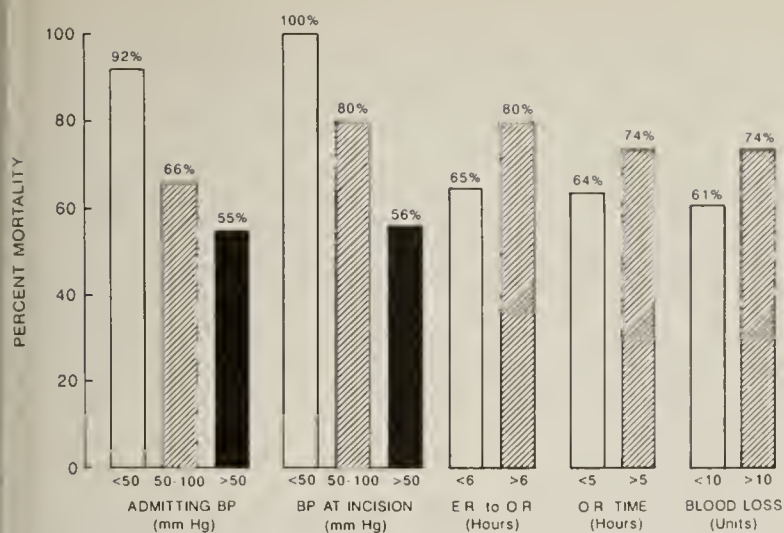


FIGURE 1. Factors significantly correlated with mortality ($p < 0.05$).

whereas others^{5,8-10} corroborate our findings that admitting blood pressure is an important determinant of survival.

To our surprise, a time interval of less than six hours from arrival at the hospital to skin incision did not correlate with survival. Only when the groups were divided into those operated on less than or more than six hours from arrival to incision was there a significant difference in survival. Meyer et al¹¹ reported similar findings, with a mortality of 100% when surgery was delayed more than six hours. In that series, patients operated on within two hours of presentation had a significantly higher mortality. Our data also showed a very high mortality for patients operated on within two hours (Table III). Vohra et al⁶ reported that delay improved survival. In that group, unstable patients reached the hospital faster, whereas the more stable patients were referred from outlying hospitals. This "self-selection" of the more stable patients may play a role in the improved survival, since patients operated on early are those in shock and who have the poorest prognosis. Speed in delivering these patients to the operating room may be important in some cases, but its relative importance is overshadowed by the patients' initial blood pressure. Regardless of speed in providing surgery, most of the patients with profound hypotension die. Johnson et al⁵ reported that despite an aggressive approach to RAAAs with immediate surgery in all patients, survival did not increase. He suggested that delay in the stable patient, with time adequately to prepare the patient, may be better therapy.

Interestingly, we did not find a correlation between patients' age and survival (Table II). Some authors^{6,7,12,13}

TABLE III. Mortality as Related to Time from Patient Arrival In Emergency Room to Abdominal Incision

Time from Emergency Room to Operating Room (min)	Mortality
0-1	72% (13/18)
1-2	79% (15/19)
2-3	57% (4/7)
3-4	33% (3/9)
4-5	75% (3/4)
5-6	33% (1/3)
>6	80% (8/10)

TABLE IV. Time In Operating Room Versus Mortality

Time (hr)	Mortality
<1	100% (5/5)
1-2	82% (9/11)
2-3	60% (6/10)
3-4	48% (10/21)
4-5	73% (11/15)
5-6	75% (3/4)

have also noted that age was not a significant predictor of mortality, whereas others¹⁴⁻¹⁷ have reported age as an important discriminant of survival. Donaldson et al⁹ reported a significant increase in mortality in patients over the age of 76 years, whereas mortality in the study presented here was lowest in this age group.

Time in the operating room of more than five hours and blood loss of more than ten units correlated significantly with increased mortality. This is not surprising and has been noted by others.^{7,12,18} Similar to the results in our series, Vohra et al⁶ found a significant mortality for patients transfused with more than ten units. In that series, 100% of patients died if they received more than ten units of blood, whereas only 34% who received less than ten units died.

Both time in the operating room and blood loss, not surprisingly, correlated with technical and potentially avoidable problems. Mortality was also greater when a large group of general and vascular surgeons was responsible for operating on the ruptured aneurysms. Some of these surgeons had had very little prior experience in this type of procedure, and for many this was the first RAAA they had ever repaired. When only six vascular surgeons operated on the ruptured aneurysms, the mortality decreased to 54%; however, one surgeon had operated on the majority of these cases. These results seem to indicate that a smaller number of surgeons repairing RAAAs increases survival among patients with a good probability of surviving. Other authors have reported a significantly higher mortality with technical complications.⁹ Jenkins² suggested that concentrating the surgical experience for ruptured RAAAs among a small group of surgeons improved survival significantly, compared to the results found where many general and vascular surgeons perform the surgery. They reported that having a small group of surgeons eliminated technical errors associated with the steep "learning curve," and that in "few other areas of surgery is experience so directly reflected in survival rates."

We conclude that patients profoundly hypotensive on admission or at the time of incision are unlikely to survive regardless of other factors, patients with a blood pressure greater than 100 mm Hg have the best chance of survival, a delay of up to six hours in patients with a blood pressure greater than 100 mm Hg does not increase mortality, and a smaller number of surgeons operating on most of the RAAAs increases survival. Based on these observations, we advocate that patients with a suspected RAAA and a blood pressure greater than 100 mm Hg be brought to centers with surgeons experienced in RAAAs, or that they be transferred to such facilities within six hours, and that such centers designate specific surgeons with an interest in RAAAs to develop the expertise to handle these cases.

Hospitals and surgeons transferring such patients should recognize that it is not known whether the additional time required to transfer these patients will actually alter the outcome, and some patients may actually die en route.

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ABDOMINAL AORTIC ANEURYSM

Before the advent of reconstructive arterial surgery, aortic aneurysms carried a poor prognosis as shown by statistical studies of long-term survival rates. In contrast, since 1951 when Dubost, Allary, and Oeconomos achieved the first successful excision of an abdominal aortic aneurysm with graft replacement, the outlook for this condition has radically changed as reflected by the vast experience accumulated in the past fifteen years. As a result of the impressive surgical achievements, indications for excisional therapy have been widely accepted for the majority of, if not all, cases of abdominal aneurysms.

... Our personal experience includes a number of cases in which rupture was the first manifestation of a previously completely silent aneurysm. From analysis of the previous data, it is clear that the absence of pain and small size of the lesion characteristic of an asymptomatic aneurysm are not reliable prognostic indices. Other factors should be weighed carefully in assessing surgical indications.

Ruptured aneurysms. Rupture of an aortic aneurysm is a catastrophic event, posing urgent problems in diagnosis and management. Successful outcome will depend on prompt recognition and precise and rapid surgical management. The incidence of ruptured versus nonruptured abdominal aortic aneurysms varies widely as reflected by a few published reports. In their most recent report on this subject, DeBakey *et al.* state that 8 per cent of their cases had ruptured aneurysms. In our own series, 24 per cent of the aneurysms were referred to us in this condition. Lack of prompt recognition and delay in admitting patients to the hospital may account for this high incidence. Greater awareness of the diagnosis and immediate referral by the general practitioners and internists will help to reduce this dreadful and often fatal complication.

Rupture into the retroperitoneal space. The most common site of rupture of an abdominal aortic aneurysm is in the posterior wall, about 1 to 2 inches distal to the renal vessels. Extravasation of blood remains retroperitoneally, at least in the initial stage. Some patients may die at the onset, but most of them survive and remain alert for at least a few more hours. This lucid interval may last one or more days. However, the pain will often progress to involve the left flank with radiation into the groin or scrotum which may lead to confusion in some cases with ureteral stone. Examination usually discloses mild or severe shock and an enlarging pulsatile abdominal mass. Shortly after the onset, these patients may become oliguric or anuric. Prognosis is hopeless in the majority of cases.

Rupture into the inferior vena cava. Rupture of an abdominal aortic aneurysm into the inferior vena cava is an uncommon complication. However, in recent years several cases have been reported. As a result of widespread use of aortic surgery, many more cases were diagnosed and treated successfully. . . .

HENRY HAIMOVICI, MD
(*NY State J Med* 1967; 67:691-701)

Glénard's disease: The vagaries of visceroptosis

THOMAS S. N. CHEN, MD, PETER S. Y. CHEN, MD

Visceroptosis, also known as Glénard's disease, provided a medical paradigm at the end of the 19th and the beginning of the 20th centuries. For physicians on the Continent and in Great Britain and the United States, the concept of problems arising from organs displaced from their usual anatomic sites accounted for the supposed pathogenesis of a host of gastrointestinal and extragastrointestinal disorders. Although it was Franz Glénard (1848–1920) who first codified the doctrine of visceroptosis in 1885,¹ others contributed to its formulation.

THE MOVEABLE KIDNEY

During the 17th and 18th centuries, dissection of the human body became an accepted and routine procedure in medical education and clinical practice. Physicians began to record the variations in the anatomic sites of organs, initially the kidneys and then others, and some clinicians proceeded to speculate on a relationship to symptoms and illnesses. Antedating this period, credit for the earliest observation of a displaced organ belonged to Johannes Mesuë (ninth century) of Baghdad. He attributed the downward dislocation of the kidney to jolting that caused the stretching or rupture of the renal attachments.²

Jean Riolan, who disputed Harvey's theory of the general circulation of blood, noted in 1682 that the kidneys could move forward and downward into the abdominal cavity as the result of the loss of perinephritic fat or from an increased renal weight from tumor or stone formation. Matthew Baillie (1793), the English pathologist, was among the early clinicians to relate renal ptosis to clinical findings in a patient.² Pierre-François-Olive Rayer (1837–1841), a prolific French physician and author, compiled seven cases of nephroptosis in his three-volume treatise on diseases of the kidney.³ He believed that the condition was commonly overlooked and misdiagnosed as hypochondria and sciatica. He observed that the right kidney was more likely to prolapse than the left, and he assumed that pregnancy and heavy lifting were among the etiologic factors. Rayer recommended bed rest and abdominal binders for treatment of the disorder.

A notable complication of nephroptosis was elucidated by Josef Dietl of Cracow who, in 1864, reported on the crisis associated with twisting of the renal pedicle.⁴ The

symptom complex of acute lumbar pain, nausea, vomiting, chills, fever, and shock has since carried Dietl's name. Aside from local effects, such as hematuria, albuminuria, and hydronephrosis, clinicians assigned general symptoms to the prolapsed kidney as described by one surgeon:⁵

The morbid phenomena due to the moveable right kidney in its earliest stages are: digestive disturbances, chronic in character; general nervousness; epigastric pain, usually located somewhat to the left of the median line, at or near the free border of the left costal cartilages; cardiac palpitation; inability to feel comfortable or to sleep when lying on the left side.

The moveable kidney, however, did not command general and widespread recognition as a nosologic entity until the rise of renal surgery in the late 19th century. In 1881, Ernest Hahn of Leipzig introduced nephropexy as a relatively safe operation.⁶ The reported incidence of renal ptosis increased precipitously, and was accompanied by radical cures with various types of surgical procedures.⁷ It was not until the 1930s that ineffective operations for a then discredited disorder faded away. As late as 1939, urologists continued to affirm the occurrence of symptomatic nephroptosis and its cure by nephropexy.⁸

THE DISPLACED LIVER

Concurrent with the rise and fall of the moveable kidney fad was the parallel career of a companion entity, the displaced liver. Early autopsy descriptions of the malpositioned liver were recorded by, among others, Lorenz Heister (1754), F. B. de Sauvage (1768), and Antoine Portal (1804).⁹ Arnaldo Cantani of Naples (1866) provided the first clinicopathologic correlation of the floating liver in a woman.¹⁰ Somewhat later, two extensive monographs, Leopold Landau's *Floating Liver and Pendulous Abdomen in Women* (1885) and Franz Glénard's *On the Mobility of the Liver* (1896), established the nosologic existence of the condition.¹¹

Proponents agreed that the contributory factors in the development of the moveable kidney, such as loss of abdominal muscle tone due to tight lacing from corsets or pregnancies, and weakness of fixation ligaments and support structure due to trauma or congenital defects, also pertained in cases of hepatoptosis. Aside from local pain and discomfort, displacement of the liver may kink the duodenal outlet, resulting in dilation of the stomach with attendant dyspepsia, gas accumulation, and maldigestion. Jaundice and gallstones were also thought to arise from the kinking of the common bile duct. Compromised liver

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function, termed hepatism by French authors, was thought to lead to general disorders such as diabetes mellitus, rheumatism, and neurasthenia.¹²

The treatment of hepatoptosis, considered at best a difficult task, consisted of extended bed rest and the use of abdominal binders. Lacking a safe surgical cure, the diagnosis of floating liver posed a lesser therapeutic threat to the patient than that of renal ptosis, although it also occupied a place in the medical thinking of contemporary physicians.

FRANZ GLÉNARD AND VISCEROPTOSIS

The preceding works on the prolapse of the liver, kidney, and other organs (not discussed here is the uterus, which has its own voluminous literature) converged in a grand synthesis by Franz Glénard (1885) in his concept of enteroptosis.¹ Later, the more general term visceroptosis (1899) replaced enteroptosis, although the meaning did not change.¹³ Glénard, born in Lyon, France, in 1848, spent time during the Franco-Prussian War (1870) as a prisoner of the Germans, from whom he learned the practice of cold baths in the treatment of typhoid fever.¹⁴⁻¹⁶ He earned considerable notoriety when he introduced the same practice in France. Glénard devoted the bulk of his professional career to the care of patients at Vichy. The resort area there attracted patients from all over France who came to take a mineral water cure. The examination of a large number of neurotic persons convinced Glénard that the root of their problem lay in the gut. It was in such a setting that he evolved his theory of visceroptosis.

Glénard wrote extensively on this topic and on the liver, in particular the physical diagnosis of liver disorders and hepatism (Fig 1). Within a decade of his initial paper on enteroptosis (1885), Glénard's disease became a common term in the medical circles of Europe and America.¹⁷ Glénard died in 1920, well revered as a physician. He left a son, Roger Glénard, who carried on his work on hepatism.¹² During Glénard's lifetime, visceroptosis became synonymous with neurasthenia (also known as "the American disease").¹⁸

In his practice at Vichy, Glénard uncovered 148 cases of visceroptosis among 1,310 patients (11% incidence). Almost all the patients with visceroptosis complained of neurasthenic symptoms. His contemporaries readily accepted the thesis of a link between the dysfunction of the gut and the mind. Such an identity was indicated by the usage of the terms intestinal neurosis and nervous dyspepsia. A strong association was made between anxiety neurosis and Glénard's disease.¹⁹

According to Franz Glénard, visceroptosis was initiated when the suspending ligaments of visceral organs became relaxed.²⁰ The disorder began with prolapse of the right colon due to stretching of the weak hepatocolic ligament. The ascending and transverse colons sank down, leaving the left colon held up by the strong gastrocolic ligament. The acute angle produced at this point supposedly led to an empty transverse colon that became contracted and firm. The low right colon also pulled down the greater curvature of the stomach, creating a kink between the first and second portions of the duodenum. This led to obstruction, dilation, and ptosis of the stomach. The mesentery of the small bowel weakened, in turn dragging down the



FIGURE 1. Franz Glénard palpating the liver (reproduced from Glénard,¹² courtesy of the New York Academy of Medicine).

spleen, liver, and kidneys.

Glénard delineated several signs of visceroptosis: splashing sound elicited over the prolapsed and dilated stomach; pulsation of the aorta palpable over the area uncovered by the descent of the stomach; "corde colique transverse" (Glénard's sign), felt as a ribbon-like body across the navel; and a moveable kidney detected in the right hypochondrium. Symptoms arose during the three phases of the disease process. During the first stage (atonie gastrique), the patient ate everything but experienced slight dyspepsia, mild somnolence, and gradual loss of strength. In the second stage (mésogastrique), the patient avoided fatty food and complained of a dragging sensation in the abdomen. Sleep became disturbed. Stool evacuation was infrequent, and fatigue increased. By the third stage (neurasthenique), the patient lost considerable weight. Constipation was obstinate. Severe generalized weakness ensued, along with various nervous symptoms.

For Glénard, there was no cure for the patient with visceroptosis. Adequate nutrition, regulation of bowel movements, exercise, and an abdominal bandage to raise the intestine and increase intra-abdominal pressure alleviated the symptoms.

ATTEMPTS TO TREAT VISCEROPTOSIS

The believers in Glénard's disease expanded and modified the original description, particularly with regard to etiology and treatment. For many physicians, the primary factor in the pathogenesis of visceroptosis was diminished intra-abdominal tension, principally from a lax abdominal musculature, but also from loss of intra-abdominal fat and

a weakening of the pelvic floor.^{21,22} This led to an upset in the equilibrium of visceral organs and to their descent. Others thought that an alteration in the interplay of muscles of inspiration and expiration forced the viscera downwards.²³ The prolapse of the viscera produced kinking of the gut at two points, the duodenum and the left colonic flexure. The retarded intestinal flow promoted not only malnutrition but stasis. On the basis of the latter, a whole school of clinicians developed the hypothesis of intestinal auto-intoxication.²⁴ The absorption of toxic proteolytic products of stagnant feces was thought to cause a host of symptoms. In addition to malnutrition, the neurasthenic effects of visceroptosis were attributable to a "... devitalizing of the sympathetic system in which vitality of the neuro-vascular visceral pedicle is impaired, it becoming elongated, stretched."²⁵

The major predisposing conditions associated with weakened abdominal and thoracic musculature were pregnancy and the wearing of corsets. The consequence of corsets and their baleful effects drew much medical attention (Fig 2).²⁶ Dickinson,²⁷ using manometric methods, quantitated the effect of corset use, concluding that

The estimated total pressure of the corset varies between thirty and eighty pounds. . . . The circumference of the waist is no criterion of tightness. . . . The capacity for expansion of chest was found to be restricted one fifth when the corset was on. . . . The thoracic character of the breathing of women is largely due to corset wearing. . . . The abdominal wall is thinned and weakened by the presence of stays. . . . The pelvic floor is bulged downward by tight lacing one third of an inch.

In men, and in young women not wearing corsets, constitutional weakness of supporting tissue was held to be the important pathogenic factor.²⁸

The treatment of individuals enfeebled by multi-organ symptoms, as in visceroptosis, taxed the ingenuity of physicians, who rose to the occasion. One popular regimen, the Weir Mitchell rest cure (1875), which was devised initially for the treatment of nervous ailments,²⁹ consisted of absolute bed rest for four to eight weeks, general massage preceded by a cool bath, exercise to strengthen abdominal muscles, raising the thorax up by proper posture and exercise, feeding to relieve the anemia and build up abdominal fat, and training of the mind and body by conscious mental efforts.³⁰ The details were outlined by S. Weir Mitchell in his aptly titled monograph, *Fat and Blood and How to Make Them* (1877). Among other interventions, Carl Anton Ewald, one of the founders of modern gastroenterology in Germany, proposed intragastric faradization to treat the functional disturbance of gastropnoptosis, which he considered to be the major element of visceroptosis. The subject of abdominal support by corsets, binders, and bandages generated a controversy on appropriate devices and techniques of application.³¹ No less contentious was the matter of surgical relief. Which organ to fix and what procedure to do puzzled the minds of surgeons and challenged their skills.³²⁻³⁴ The occasions for excesses and ineffectual operations appeared unbounded. At least one such operation, colectomy for the cure of intestinal auto-intoxication, has been well documented.²⁴

BODY HABITUS AND DISEASE

Berthold Stiller, an Austrian contemporary of Glénard, discovered that all patients with visceroptosis presented with a floating tenth rib (Stiller's sign). In fact, the disorder was part of a syndrome which he called "asthenia universalis congenita." The title encapsulated one of Stiller's and his followers' favorite themes, the relationship of body habitus and disease. Physicians of this school employed anthropometric measurements to confirm the postulate that an asthenic person with a narrow thorax and elongated abdomen had a predisposition to organ prolapse.

One observer described the features of habitus enteroproticus:

The first impression one gets of such a woman is that of frailness, expressed in the contour of her form and often in her features. She is slender and has but little adipose tissue; her form is angular; her muscles are thin; there is almost invariably a perceptible laxness and softness of her tissues. She impresses one as being underdeveloped and lacking in vigor. These may be designated as fundamental characteristics . . . one notes in such an individual that the neck is long, the chest undersized and showing distinct signs of collapse; that is, it is shallow, the upper ribs far apart, the lower ones slanting downward and inward and lying close together.

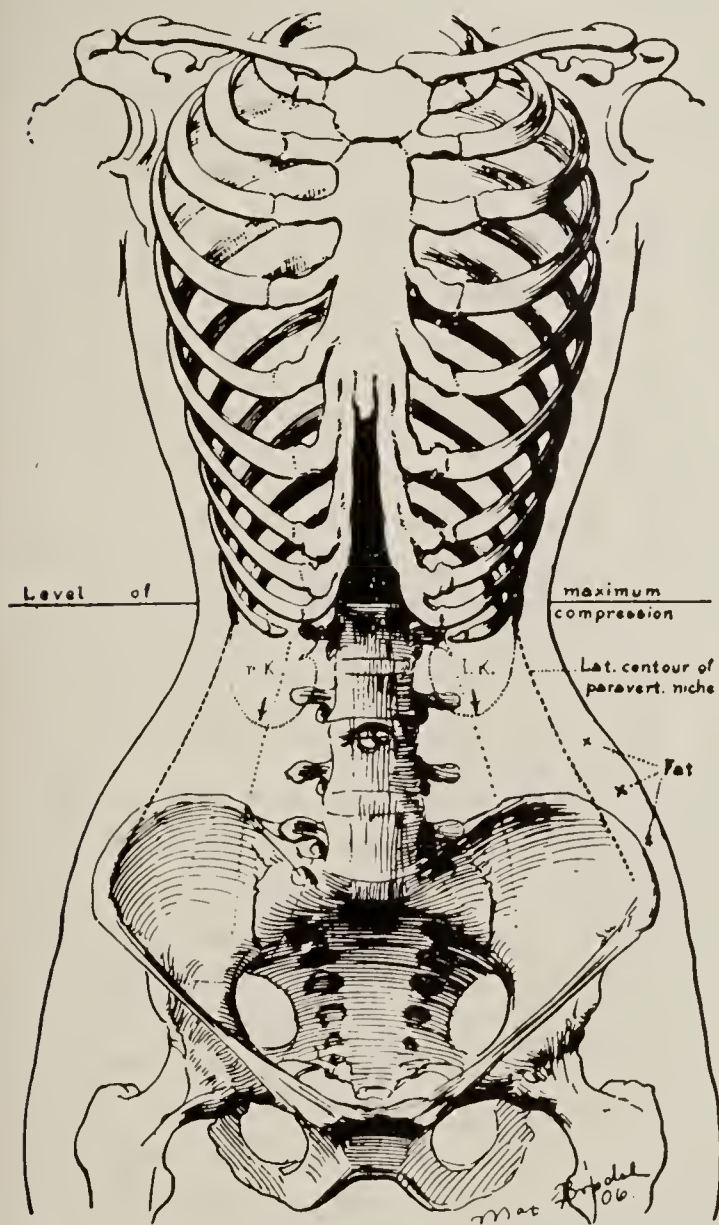


FIGURE 2. Skeleton showing the effect of corset-lacing with resultant nephroptosis (reproduced with permission from Kelly et al⁴³).

er, and there is a distinct lessening of the capacity of the thoracic abdomen. The abdominal muscles are soft and lack resistance (muscular insufficiency) and there is a tendency for them to bulge forward.³⁵

In practice, some clinicians used an objective test for the detection of ptosis: the Becker and Lanhoff body index (distance from suprasternal notch to symphysis pubis over the circumference of the waist, divided by 100).³⁶ A figure over 77 meant a high likelihood of the presence of a moveable kidney.

DISAPPEARANCE OF VISCEROPTOSIS

Judging from the number of publications, visceroptosis attained its highest vogue during the 1910s.³⁷ This period also witnessed the acceptance of radiographic examinations in both the clinical and investigative settings. Early radiologic studies appeared to support the idea of organs in descent (Fig 3).³⁸ However, careful investigations based on similar radiologic techniques demonstrated a range of organ locations in healthy persons.³⁹ The new understanding of gastrointestinal physiology controverted the hypothesis that the moveable position of visceral organs affected their function. Within a decade of Glénard's death, visceroptosis became untenable as a disease with all its attributable symptoms.

Among deceased diseases, visceroptosis had a short life span, about two generations, similar to the other entities that grew up and succumbed during this century.^{40,41} In a wonderful paper on this topic, Beeson⁴² has summarized the reasons for the disappearance of diseases:

(1) Social or environmental changes could eliminate a necessary condition. Possibly milk sickness and chlorosis belong in this category. (2) A syndrome previously thought to represent a single "disease" comes to be recognized as something common to several quite different pathologic processes. This appears to fit Miku-

licz's disease and agranulocytic angina. . . (3) A hypothesis concerning pathogenesis, based on inadequate information, proves to be erroneous. Here we could place status thymicolymphaticus and Ayerza's disease. . . (4) A valid, but rare, relationship comes to be too frequently suspected, leading to undesirable clinical practice, and causing unnecessary anxiety on part of doctor and patient. This would seem to apply to Fröhlich's disease. (5) A disease could really disappear after recognition and elimination of a specific cause. Thus, the most common cause of agranulocytic angina in 1930—the analgesic amidopyrine—has departed from the scene. (6) An infectious agent can undergo mutation . . . examples of this include the case of influenza viruses, and it is conceivable that the mysterious appearances and disappearances of the English sweating disease, miliary fever, and encephalitis lethargica can be ascribed to changing characters of infectious agents.

To this list we may add visceroptosis. It faded away because its underlying hypothesis was based on evidence that turned out to be untrue. Visceroptosis became discredited as it no longer served as a nosologic paradigm for the medical Zeitgeist.

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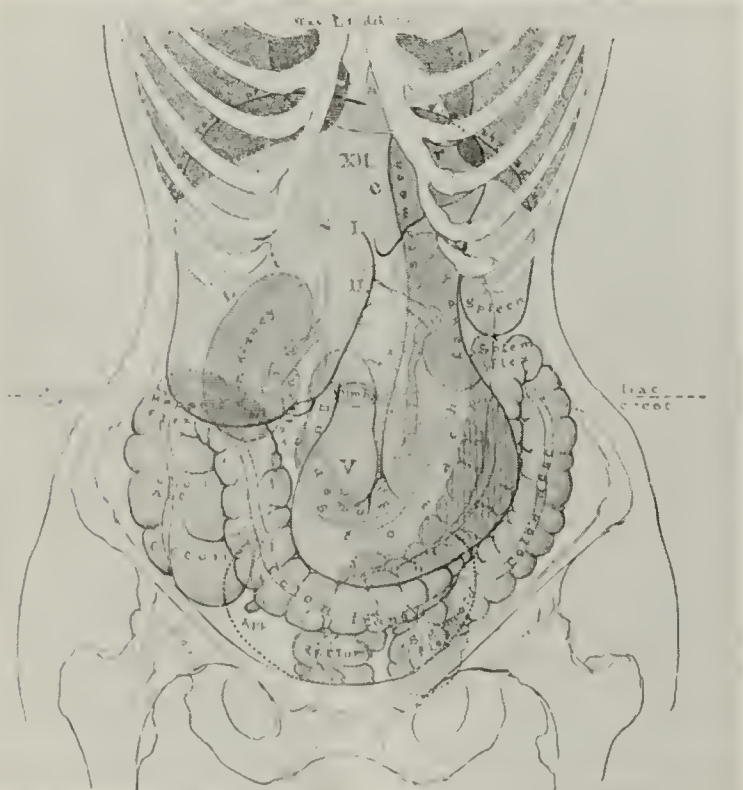


FIGURE 3. Schematic representation of the positions of visceral organs in visceroptosis, based on radiographic studies (reproduced with permission from Kelly et al⁴³).

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FROM THE LIBRARY

GLENARD'S DISEASE

Glenard's disease, abdominal, or visceral ptosis, is no new disorder, and yet the last word has not been spoken upon it, and may not be for a long time. In fact, like the poor, it is always with us, and this is not intended as a pun, even if many of these patients are quite emaciated.

The symptom complex was described a number of years ago, and while I shall consider it as a condition rather than a disease, I do not wish to overlook the complex character of its symptoms, or its fundamental causes, and I am persuaded that only a feature or two are recognized by the physician, and that feature is dictated more by the point of view from which the physician sees the patient than the importance of the feature in question.

It is my purpose to review from the standpoint of experience and observation this condition, and to briefly outline what has been in my hands a successful method of treatment in many cases which had survived often long periods of treatment of various sorts, with at best indifferent results, before they came under the regime referred to.

First then the condition: A poorly nourished patient (not necessarily anaemic), usually under weight, muddy complexion, with rings under the eyes, complains of tiring easily, headache, gas in stomach after eating or even while eating. Appetite poor, or if hungry is satisfied before a reasonable amount of food has been eaten, complains of cold extremities, especially at night, usually constipated bowels and on inquiry we will often find insufficient action of kidneys, sleep broken and dreamy and to these symptoms are often added palpitation or tachycardia, depression, a mental state of apprehension as of some impending evil and not infrequently in the case of mothers, a feeling as if they could not stand the prattle of the children. . . .

Etiology.—The fundamental cause of abdominal ptosis, or at least the most frequent cause is heredity. That is, most of these patients were born with a poor nervous endowment, and if we take up the causes in the order of the development or growth of the patient as well as the frequency, we must recognize next rapid eating and over filling the stomach during early childhood.

I believe that abdominal ptosis, or at least gastropptosis, is very frequent in children from the fifth to the twelfth year, usually unrecognized and generally coming back to normal as the child takes up more athletic exercise or an occupation which develops stronger abdominal muscles.

Next in order comes the period of adolescence, when the young person is acquiring the sedentary habit and developing latent neurasthenia and upsetting digestion in the endeavor to keep pace with the high school hours and examinations.

It is during this period when the nervous mettle of these poorly endowed, though often brilliant persons, receives its first severe strain, and not very infrequently it proves unable to meet it. . . .

Now the distresses reach a point which finally drives the patient to the physician, with varying results.

Treatment.—The treatment then which will prove successful must take into consideration the nervous constitution and the inefficient muscular support brought out by the physical inventory, and must aim to increase the physical endowment and the abdominal muscular strength. . . .

The prescribing of such a regime may seem easy, but its success depends on experience and the courage and conviction to secure the cooperation of the patient, and the physician must see the patient frequently enough to keep up his co-operation and courage until he can see results. Then things will move on more smoothly and less personal attention will be required.

BRADFORD C. LOVELAND, MD
(*NY State J Med* 1916; 16:250-253)

Health advice from other days

LEO J. KOVEN, MD

When I was growing up in the 1920s, health was a regular subject of discussion. Children were constantly exposed to warnings from their elders that were virtually identical in every home. To follow all the precepts laid down was the path to good health, but woe to the child who did not heed the rules. We were taught to believe that our survival was due to the wisdom of those days which was a time tested hand-me-down from previous generations. Repeated often enough and assertively by our parents and others, this wisdom acquired the imprimatur of truth while remaining deep down for the most part baseless. Fortunately, in defying authority we really did not put ourselves at significant risk.

When I was a child and happened to fall ill my mother would repeat to herself, sotto voce, "starve a fever and feed a cold." Most often she dispensed with the thermometer and used much honored and presumably infallible measuring devices. After looking for red blotches on my burning cheeks she would then press her lips to my brow. Having determined by these tests that I had a fever, my feedings were drastically restricted, if not totally denied.

Nevertheless, confusion reigned. Was it "fever-starve" and "cold-feed," or "fever-feed" and "cold-starve"? She was never quite sure and was joined in her uncertainty by the mothers of the neighborhood. Nor were these alternating dicta, with their frequent reversals, particularly clarified by a host of relatives and friends who happened to be physicians. Each doctor made oracular pronouncements with an air of certainty. They might have been frequently wrong, but were seemingly never in doubt. What was the rationale? Could some scientific verification be invoked or was anecdotal folklore at work here?

One day it occurred to me that most often my colds were associated with some degree of fever. In such a circumstance how was I to be concomitantly both starved and fed? Unable to solve the dilemma I turned to my mother, seeking a solution to the conflict. Her answer was an off-putting, "I'll explain it to you when you are older." In the meantime I had premonitions of developing skeletal-like thinness or overwhelming obesity. Yet I was fortunate in surviving my childhood without suffering either.

One day at school my fourth grade teacher broke up a shoving melee. She was an enormous woman who at every opportunity informed the class that she was descended from Vikings, and had been born in Iceland. Her size

dominated the room and, along the way, our behavior as well. She issued edicts and had us repeat them. For example, the boys were made to swear "never to hit girls on the chest or backside, for it would give them cancer!" I came home and questioned my mother about this. Not only did she confirm the truth of the statement, but she also found frequent occasions to repeat it to me, particularly when a dispute with my sister showed signs of deteriorating into a physical encounter.

Did this mean that girls could strike boys with impunity because their maleness carried with it an inherent immunity to traumatically induced cancer? Going a step beyond, were boys permitted to assault the opposite sex on the limbs, abdomen, or head without fear of drastic complications? Anyway, what the heck was a cancer? Apparently it was some horrible affliction to which the female breast and buttocks were prone on being struck. Yet, hadn't I seen my mother administer a spanking to my sister? Perhaps mothers had a safe way of applying the blows, and boys were not privy to its secret. What should have been a matter of chivalry was reduced to a fear of the consequences of defying Miss Ericson's, and my mother's, injunction.

While speaking of violence, I recall that my teachers and parents (and what greater repositories of wisdom could there be) frequently warned us "never to hit a kid with glasses." Our neighborhood bully (each neighborhood seemed to have had one) resolved the issue with simple and impeccable logic. In the course of a dispute as to whether he had tagged Little Jimmy as he rounded the bases, he grasped his arm, while the rest of us implored him not to strike our bespectacled playmate. He tightened his grip on Jimmy, and in response to our warning, demanded that Jimmy remove his glasses so he could give him a good whack. The poor kid was frozen with fear and terror, so the bully knocked off his glasses and struck a telling blow to his solar plexus, the area we knew to be our hero Jack Dempsey's favorite and most effective target. The rest of us, lacking the bully's uncontrollable aggressiveness, continued to abide by the rule against attacking anyone "four-eyed" as we then called them. Yet, on occasions when one of us caught Jimmy not wearing his glasses he was at our mercy.

Food was considered vital to good health and our parents often cited examples of those suffering from famine in order to get us to eat. For example, they would say "think of the poor starving Armenians and clean your plate." What was an Armenian? I had never seen or met one.

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What did they look like, and why were they starving? Would cleaning my plate cure, or at least mitigate, their starvation? This was indeed a quandry.

There was even more to the issue. Dessert was only given to "empty platers." Yet, if much hated spinach or liver were offered, even citing the suffering of the Armenians had no effect. My mother went into a face-saving retreat from the empty plate-dessert threat. Now it became "Just one (or two or three) more spoonfuls." The compromise saved face for both of us and dessert could be had.

By the time I grew up and had children of my own, the Armenian famine had disappeared from our aphorisms. Now it became "Popeye eats his spinach and it gives him muscles." This never achieved the results of the Armenian aphorism, but the old chestnut of "just one more spoonful" still worked its magic.

Wet, cold, dampness, and drafts were inevitably associated with respiratory illness. In the wisdom of those days I had to take off my wet shoes immediately on entering the house after playing in the snow or sloshing through puddles. I would then be chastised for not wearing my rubbers or galoshes. I can't think of any other objects that were more anathema to a boy's self-image. Wearing those hated objects was in our minds a sure indication of sissiness. We could not be deterred by the threat that we would "catch our death." It was too remote an abstraction for us

to conceive of. In the same vein, cold floors demanded that we wear our slippers because "cold feet today mean a running nose tomorrow." Apparently feet lacking an appropriate measure of warmth struck back by causing illness. Perhaps most dangerous of all in assaulting one's lungs was sitting in a draft. Everyone knew that "sitting in a draft brings pneumonia." To make matters even worse, to do so while heavily perspiring after coming in from hard play made the dreaded consequence a certainty.

How did I survive all these assaults on my pulmonary system, and particularly in an era when antibiotics were as yet unknown? Perhaps there was then some broadly present inborn immunity. Yet I think it was because the theories of causation then current had the fallibility of anecdote, and lacked demonstrable veracity.

We, well most of us anyway, survived the rigors of childhood without inanition, cancer, corneal laceration, pneumonia, and the like. We were not an especially hardy race but we were children making our way free of the faulty logic of the adult world which surrounded us. This perhaps was useful for our survival. We appear to have had some inherent wisdom that defied that of the adult world. We were resisting authority as children of all ages had done and shall do. I wonder if any of the shibboleths we pass along in this generation may suffer a similar, and perhaps just as well deserved, fate.

Interstitial cystitis

CIRIL J. GODEC, MD; ADLEY RABOY, MD; IVAN GRUNBERGER, MD

The symptom complex of interstitial cystitis is not specific and overlaps with that of a variety of painful bladder diseases. Frequency of urination, urgency, nocturia, and suprapubic pain represent the main diagnostic features. Urinary incontinence is rare. The symptoms vary in intensity from mild to severe and unrelenting. The milder forms of interstitial cystitis are difficult to separate from urethral syndrome, non-specific cystitis, and urethritis. The milder symptoms usually appear in the early stage of the disease; the classical or late stage has the same symptoms, but with greater intensity.

Interstitial cystitis is one of the most frequently overlooked urologic diseases. A recent study conducted jointly by the Urban Institute in Washington, DC, and the Interstitial Cystitis Association documented a significant delay in diagnosing this condition, with an average of seven years between the onset of symptoms and the final diagnosis.¹ The same survey documented that 40% of women with interstitial cystitis were unable to work, 58% were unable to have intercourse, and 28% ended their relationship with their spouse or significant other. Another 12% of the respondents in the study had attempted suicide, and more than 55% had considered suicide more than once in the course of their disease. Frequently, these patients are sent from one physician to another, most often to urologists, psychiatrists, gynecologists, orthopedic surgeons, and internists.

The case presented here demonstrates that many of these patients often undergo unnecessary surgery, which provides no improvement and no clearer diagnosis. Many patients are ultimately referred to a psychiatrist by a frustrated practitioner who believes

that the symptoms must be psychosomatic, or the visit to a psychiatrist may be initiated by the patient herself who believes that she is losing her mind.

CASE REPORT

A 29-year-old woman, gainfully employed and steadily progressing in her career, was referred to our office with a chief complaint of suprapubic pain which had been present for the past nine years. Seven years previously, the patient had undergone a right oophorectomy for pelvic discomfort. The pain did not subside, and an oophorectomy was performed on the contralateral side one year later. Due to persistent pelvic pain, the patient underwent a hysterectomy two years later, with no relief of pain. Only occasional temporary relief followed treatment with antibiotics for what were termed recurrent urinary tract infections, though must urine cultures were negative. On further questioning, she gave a history of intermittent episodes of marked daytime urinary frequency, with voiding nearly every hour during the day. Surprisingly, she rarely complained of nocturia. Her suprapubic pain was steady, though worsened when the bladder was full. Analgesia provided little relief. She had no complaint of either urge or stress incontinence.

On physical examination, the only positive sign was significant pain at the base of the bladder during the pelvic examination. The patient's urinalysis and urine culture were negative. Three urinary cytologic studies were negative for malignant cells; cytologic grading varied between class 1 and 2. Cystoscopy under general anesthesia revealed an essentially normal bladder; no ulcers were seen. The bladder capacity was 400 cc. After distention with 80 cm of water pressure, diffuse petechial oozing, or "waterfall bleeding," was seen. Four random biopsies were taken, and histologic analysis showed chronic cystitis (Fig 1).

Staining for mast cells was positive with toluidine blue. The patient underwent four intravesical treatments with 50% dimethyl sulphoxide, 50 cc for 15 minutes. Remission of her symptoms, for the first time in nine years, was achieved. For the following two years, the patient had occasional suprapubic pain, but did not require additional treatment.



FIGURE 1. Toluidine blue stain for mast cells documents their presence in the submucosa (see arrow).

DISCUSSION

Interstitial cystitis is a common form of painful bladder disease. Although it was first described by Hunner² almost 80 years ago, it remains a poorly explained entity. Hunner described an actual ulcer of the urinary bladder. On cystoscopic examination, the ulcer is rarely seen in patients complaining of interstitial cystitis. An ulcerative lesion is frequently overdiagnosed and can be iatrogenically produced by the collapsed bladder hitting the cystoscope during cystoscopic examination. In 1975, Oravisto³ reported the incidence of the disease to be 18/100,000 in the female population of Helsinki, Finland. He found that the disease did not progress steadily. For most patients it reached a plateau and remained at that level. The majority of patients with this disease are female, with only 10% being male.⁴ Epidemiologic data are not available yet for the United States, though very likely they will parallel the findings from other countries.

The etiology of interstitial cystitis is unknown. Urine cultures are usually negative, although occasional positive cultures do not rule out the disease. If pathogenic organisms are found, there is no consistency in the type of urinary pathogen. One can speculate that the disease is produced by some pathogens that are missed in routine cultures.

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However, chronic sterilization of urine with broad spectrum antibiotics usually does not produce improvement in the course of the disease. Maskell⁵ isolated some fastidious pathogens in patients with interstitial cystitis, but such a finding may be more circumstantial than etiological. The most frequently quoted etiologic factor was proposed by Parsons et al⁶: that the disease starts with a defect in the glycosaminoglycans layer on the superficial layer of transitional epithelium, which allows the patient's urine access to the transitional epithelium and areas below it through the pathway of chronic inflammation. Based on very preliminary information, Gillespie et al⁷ claimed that some antibiotics could damage the protective layer of the luminal surface of the bladder.

Urodynamic testing is not diagnostic for the disease but may be helpful. From recently published data⁸ on the use of urodynamics in the evaluation of 50 patients with this disease, the maximum bladder capacity varied from 50 to 615 cc, with a mean of 287 cc. When data are analyzed and compared with the duration of symptoms, a trend was found toward smaller capacity (less than 300 cc) in patients with a longer duration of symptoms. Patients with interstitial cystitis usually have a normal uroflow and empty the bladder without any residual urine.

Urodynamics can also be used as a tool to evaluate the response to therapy. A favorable response correlates with the cystometrogram shifting to the right, with a delay in detrusor contraction and a larger functional bladder capacity.

Petechial hemorrhages, after hydraulic bladder distention with 80–100 cm of water pressure, are probably the most reliable and objective diagnostic criteria for this disease. Bladder mucosal biopsies are performed more to rule out carcinoma in situ, tuberculosis, and other disease entities than to diagnose the disease per se. The presence of mast cells in the specimen may facilitate the diagnosis, since an increased number of mast cells in patients with interstitial cystitis has been confirmed in most published reports.^{9,10} However, others¹¹ have disputed this finding.

The choice of treatment remains difficult. In milder early stages, patients may respond to anticholinergic medication. Bladder instillation of dimethyl sulfoxide is the most frequently used

and the most successful therapeutic modality, having been approved by the Food and Drug Administration (FDA) for this purpose in 1978. With low systemic toxicity,¹² DMSO provides significant anti-inflammatory activity, a direct analgesic effect, and resolution of pathologic deposits of collagen, and, at the same time, can preserve normal elastic tissue fibers.¹³ All of these properties are beneficial in the treatment of this disease. There is no one accepted treatment schedule, and at present most protocols favor bladder instillation at two weekly intervals.¹⁴

In one study in which patients received 100 mg of oral sodium pentosanpolysulphate three times per day, the study group showed a significant response. Improvement ($p < 0.05$) was noted when compared to the group receiving a placebo.¹⁵ However, this drug is not approved as yet by the FDA for treatment.

In addition, a variety of intravesical manipulations have been used to treat interstitial cystitis, including hydrodistention of the bladder. Symptomatic relief was noted in approximately 30% of patients treated with this method.¹⁶ Hydrodistention most probably causes damage to the afferent nerves and stretch receptors in the submucosa, thus diminishing pain. In another study, intravesical application of 1% silver nitrate produced improvement of symptoms in 54% of cases.¹⁷

The Nd:YAG laser has been used in 39 patients and led to improvement of symptoms, especially relief of severe pain.¹⁸ The precise mechanism of laser treatment in patients with interstitial cystitis is not known. Most likely, the sensory nerve endings are destroyed due to general tissue destruction, which occurs 2–3 mm deep into the detrusor muscle where the nerve endings are located.

Open surgery should be reserved for patients who fail conservative trials of treatment. Surgical bladder denervation¹⁹ and the different methods of bladder reconstruction with colon or ileum²⁰ have been tried. Simple augmentation and enterocystoplasty is not recommended. This procedure usually augments the bladder dome, but the remaining bladder continues to produce symptoms. Complete excision of the contracted, diseased bladder is necessary in order to achieve success. Fortunately, cystectomy and urinary diver-

sion are rarely indicated.

Interstitial cystitis is a significantly underdiagnosed disease. Many physicians, including some urologists, have difficulty in recognizing the disease as a specific entity. Diagnostic signs are somewhat imprecise and, therefore, difficult to establish. There is a need to educate the medical community about the complexity of this disease. Interstitial cystitis is a real entity that can be diagnosed and treated successfully if physicians are aware of its existence.

Acknowledgments. The authors thank Denise Schneider for her assistance in the preparation of this manuscript.

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Cystitis emphysematosa

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Cystitis emphysematosa is defined by the presence of gas within the bladder wall and lumen. It is uncommon and is seen typically in diabetics with aerobic urinary tract infections.¹ Cystitis emphysematosa should be separated from other processes that may cause gas to appear in the bladder, such as instrumentation in or near the bladder or fistulous connections between the bladder and bowel.² Approximately 150 cases of cystitis emphysematosa have been reported in the literature.¹ This report describes a patient with cystitis emphysematosa who presented with nonspecific abdominal symptoms.

CASE REPORT

A 77-year-old woman was admitted to Rochester General Hospital for evaluation of nausea, constipation, and trace guaiac-positive stool. She did not complain of dysuria, pneumaturia, or recurrent urinary tract infections. Her medical history was remarkable for gastrointestinal polyps, duodenal ulcer, diverticular disease, and osteoarthritis, for which she had been recently started on sulindac, 200 mg by mouth, twice a day. She had no history of alcoholism or diabetes mellitus.

On physical examination, the patient was afebrile, and her abdomen was diffusely tender on deep palpation. An initial white blood cell count was 13,600/mm³ without a shift to the left. A non-fasting blood glucose count was 172 mg/dL. A free air series was unremarkable.

On the second day, gross hematuria developed. The patient was otherwise asymptomatic, and her nausea and abdominal tenderness had lessened with intravenous hydration and several enemas. Urinalysis showed brown, cloudy urine with no glucose, more than 40 red blood cells per high powered field, and two to five white blood cells per high powered field. Gram's stain of an unspun sample of urine revealed multiple gram-positive rods. Several aerobic urine cultures and all blood cultures were sterile. A urine culture obtained on the eighth day, while the patient was on trimethoprim, 160 mg, and sulfamethoxazole, 800 mg by

mouth twice a day, grew 4,000 colonies of *Escherichia coli*. Unfortunately, no cultures were obtained from a spun urine sample.

An intravenous pyelogram obtained on the third day showed a distended left renal pelvis. The right kidney was not seen because of a large amount of gas in the bowel. On the fifth day, a scout radiograph of the kidneys, ureters, and bladder obtained to visualize the right kidney demonstrated a linear collection of gas in the bladder wall and lumen consistent with cystitis emphysematosa (Fig 1). A computed tomogram (CT) of the abdomen on the seventh day confirmed the diagnosis and revealed bilateral hydronephrosis (Fig 2). A supine abdominal film two weeks after admission showed resolution of the bladder gas. Cystoscopy on the following day demonstrated narrowing of the ureteropelvic junction with preserved free flow of urine into the bladder. There were no vesicles or fistulas.

The patient was never febrile, and the white blood cell count became normal after the second day of trimethoprim and sulfamethoxazole therapy. Two doses of ceftizoxime were given to inhibit possible anaerobes, since gram-positive rods were found and several initial aerobic urine cultures were sterile. While in the hospital, the patient had six normal fasting blood glucose levels, with values between 72 mg/dL and 86 mg/dL. The patient was discharged on a regimen of oral trimethoprim, 80 mg, and sulfamethoxazole, 400 mg, once a day as suppressive therapy. No anaerobes were ever isolated.

DISCUSSION

Cystitis emphysematosa has been reported in a female-to-male ratio of 2:1 and occurs most often in patients over



FIGURE 1. Abdominal radiograph demonstrating the curvilinear gas pattern along the inferior wall of the bladder (arrows). There is retained barium in the left colon.

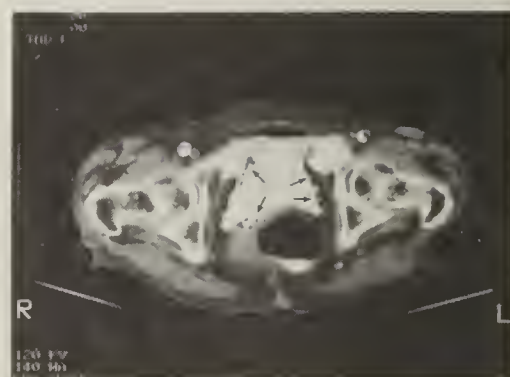


FIGURE 2. Computed tomographic (CT) scan demonstrating gas in the bladder wall and lumen (arrows).

50 years of age.² As an older woman, this patient had the typical epidemiologic background. Diabetes mellitus is an important risk factor for cystitis emphysematosa, presumably because the elevated blood sugar may provide increased nutrition for infecting bacteria.⁴ Given the six normal fasting blood sugar levels, the patient did not have diabetes mellitus. It would have been interesting to obtain an oral glucose tolerance test, since the presence of cystitis emphysematosa should raise the question of possible diabetes mellitus.

The diagnosis of cystitis emphysematosa is difficult to establish based on clinical findings. On presentation, the patient had nonspecific abdominal findings. This is not unusual since signs and symptoms, in general, may range from mild abdominal pain with or without dysuria to confusion and hypotension indicating possible sepsis.³ Pneumaturia, present infrequently, was not elicited in this case.

Hyperglycemia and glycosuria are common given the high disease incidence among diabetics. Pyuria, microhematuria, and even gross hematuria, as seen in this case, are common. Little pyuria and no hematuria may be seen.²

The abdominal radiograph is central to the diagnosis of cystitis emphysematosa. Abdominal computed tomography is also a sensitive imaging procedure for demonstrating the bladder gas.⁵ A magnetic resonance imaging (MRI) scan would have been interest-

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ing to obtain, but most likely would not have resulted in a change of therapy for this patient.

The urine grew *Escherichia coli*, the organism most often isolated. Less commonly seen are *Proteus*, *Staphylococcus aureus*, *Streptococcus*, and *Novocardia*.² Only in the rare, seriously ill patient are *Clostridium perfringens* and *Candida albicans* identified as etiologic agents.⁶⁻⁸

There have been no controlled trials to study different modes of therapy for cystitis emphysematosa. This patient's condition improved with hydration and antibiotic therapy directed against first suspected and then culture-proven bacteria. If the patient had been diabetic, good blood glucose control would have

been important.

The most recent case reports of cystitis emphysematosa have focused on the role of unusual organisms, primarily anaerobes and fungi, in seriously ill patients.⁶⁻⁸ This case reemphasizes that *Escherichia coli* is the most common microbe isolated and that the condition is usually benign. Diagnosis by abdominal radiography, appropriate antibiotic therapy, and careful blood glucose control in diabetic patients form the cornerstone for the evaluation and treatment of cystitis emphysematosa.

Acknowledgments. The author thanks Dr Scott Richardson, Department of Medicine; the Department of Medical Illustration; and the Department of Radiology of

the Rochester General Hospital.

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Persistent sciatic artery aneurysm and limb threatening ischemia

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A persistent sciatic artery (PSA) is a rare vascular anomaly resulting from failure of the embryologic axial artery of the lower extremity to regress with fetal development.^{1,2} The first recorded description of PSA was by Green³ in 1832 in an anatomic dissection. The first case documented by angiography was that by Cowie et al in 1960.⁴ While there are probably fewer than 75 cases described in the literature, this anomaly deserves particular attention because of the significant morbidity which it can cause. We describe a case of PSA with aneurysmal changes presenting as limb threatening ischemia.

CASE REPORT

A 68-year-old woman presented to the emergency room with a one-hour history of sudden onset of severe pain and numbness of the distal left leg after bending over. Her medical history was significant for deep vein thrombosis of the left leg six weeks prior to admission, for which she was taking coumadin. She had a 50 pack-year history of smoking, chronic alcohol abuse, and was on 5 mg

of prednisone a day for chronic obstructive pulmonary disease.

Physical examination revealed a cool left foot with decreased sensation to touch from ankle to toes. Motor function was intact. The left femoral and popliteal pulses were palpable with no bruits or evidence of aneurysmal dilation. The posterior tibial and dorsalis pedis pulses were absent to palpation. Pedal pulses were fully palpable on the right. Routine blood and urine tests were normal except for a prothrombin time of 16 sec. The electrocardiogram showed normal sinus rhythm with occasional premature ventricular contractions.

Noninvasive studies of the left lower extremity demonstrated a patent venous system, normal thigh arterial pressure, and no perceptible blood flow at the calf or ankle on the left. Angiography revealed a smaller than normal left external iliac artery. The common femoral artery, profunda femoral artery, and superficial femoral artery (SFA) were patent in the upper thigh but not visualized in the lower thigh. There was an aneurysm superimposed over the femoral head on frontal views. The aneurysm arose from a direct communication of the hypogastric artery and continued into the thigh (Fig 1).

The patient was taken to the operating room for planned embolectomy of the lower extremity arterial tree. In the supine position, exploration of the left groin revealed a normal appearing femoral system with no

aneurysm or atherosclerotic disease. A Fogarty catheter could only be passed 30 cm distally in the SFA; no thrombus was retrieved, and there was minimal backbleeding of this vessel. An intraoperative angiogram showed that the SFA ended in small collateral circulation above the knee. Exploration of the popliteal region through a medial incision revealed a large caliber, posteromedially displaced vessel that was strongly pulsatile. Fogarty catheter embolectomy resulted in the extraction of organized and



FIGURE 1. Right transfemoral arteriogram showing aneurysm superimposed on left femoral head in communication with left hypogastric vessel. The left femoral system is poorly visualized but appears patent in the thigh.

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fresh thrombus from the distal circulation. Antegrade popliteal angiography demonstrated a normal trifurcation with thrombus in the distal circulation. The presence of a persistent sciatic artery as the primary blood supply to this extremity was confirmed, with probable embolic debris from an aneurysm of that vessel.

A femoral-popliteal, reversed saphenous vein, above the knee bypass was successfully created. The left iliac fossa was retroperitoneally approached. An abnormally large left hypogastric artery was ligated just before it passed through the greater sciatic foramen. The popliteal artery was ligated just proximal to the distal anastomosis.

After surgery, a strongly pulsatile left gluteal mass persisted. Computed tomography confirmed a 4–5 cm PSA aneurysm with laminated thrombus (Fig 2). Postoperative noninvasive studies showed a left ankle brachial index of 0.50. The foot showed signs of demarcating at the transmetatarsal level. On the 14th day after surgery, the left gluteal region was explored. An approximately 4 × 5 cm pulsatile PSA aneurysm was partially dissected. A large feeding vessel at the sciatic foramen was ligated, and pulsations in the aneurysm ceased. The sciatic nerve was thickly adherent to the wall of the sac and no attempts were made to excise the sac. Twenty-nine days after the initial surgery, the patient underwent a successful transmetatarsal amputation. The patient is now fully ambulatory and undergoing rehabilitation.

DISCUSSION

In embryologic development, the umbilical arteries are paired fourth ventral branches of the dorsal aorta. When the embryo measures approximately 6 mm, the axial or sciatic artery has arisen from the umbilical artery and passed along the extensor surface of the hindlimb to the foot. Proximal to the takeoff of the sciatic artery, the external iliac develops, and by the 12-mm stage gives rise to the common and superficial femoral arteries. In their course of development, these vessels form communications with the sciatic vessel at the knee. Through the 18-mm and 22-mm stages the superficial femoral artery assumes the route of predom-

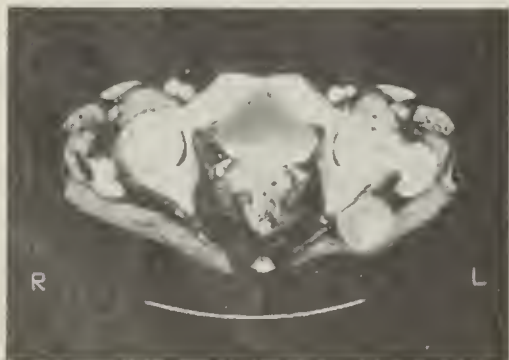


FIGURE 2. Computed tomography showing left gluteal aneurysm with laminated thrombus.

inant flow. The sciatic artery becomes discontinuous, leaving distal portions to contribute to the future popliteal and peroneal arteries. The proximal sciatic normally regresses to the extent of a nutrient vessel to the sciatic nerve and the inferior gluteal artery.^{1,5}

In a review of routine angiographic evaluation of the lower extremity, the sciatic artery has been estimated to persist in various states of its embryologic form in 0.025% to 0.04% of persons.⁶ Present in its entirety, the PSA is usually quite ectatic, coursing through the greater sciatic foramen under the piriformis muscle to enter the thigh. Here it may be in close proximity to the sciatic nerve. Running posterior to the adductor magnus under the gluteus maximus, it passes into the popliteal fossa as the popliteal artery.⁷ When "complete" in persistence, the PSA is most often the primary blood supply to that extremity. In an "incomplete" form, the PSA is discontinuous, with tributaries communicating through collateral circulation with the femoral, femora profundis, and popliteal vessels.^{8,9} When a complete PSA is present, the superficial femoral system is usually hypoplastic, but rarely entirely absent.^{1,8}

While there have been descriptions in the literature of limb atrophy, arteriovenous malformations, and other congenital anomalies associated with a PSA, the most common presentation appears to be secondary to atherosclerotic degenerative changes.^{7,10,11} Why the PSA undergoes such changes is a point of some conjecture. Positive syphilis titres have been reported in association with PSA, but this finding has not been consistent.⁹ The position of the vessel in close apposition to the sacrospinal ligament, combined with the repeated trauma of bending and sitting, has been proposed as a mechanism of degenerative change. Reduced elastic components in this embryologic hold-over has also been proposed as a contributing factor.^{2,10}

Aneurysmal dilation has been reported in 38–45% of cases reviewed.^{10,12} This leads to the most frequent symptom of pain in the buttock secondary to compression of the sciatic nerve or surrounding tissues. This presentation is followed in frequency by claudication and distal extremity ischemic changes secondary to occlusive disease and embolic debris.

The physical examination can be very rewarding if the possibility of a PSA is entertained. Pathognomonic is the finding of a palpable popliteal ar-

tery and distal pulses, an absent femoral pulse, and a pulsatile mass in the buttock region. This triad has been accurately described preoperatively only one time in the literature.⁴ The differential diagnosis of a pulsatile mass in the buttock should also include traumatic pseudoaneurysms, usually of the gluteal artery, although these are also very rare.¹³

Noninvasive evaluation may include computed tomographic (CT) scanning or Doppler examination along the sciatic nerve.¹¹ Definitive diagnosis relies on angiography. The internal iliac artery is usually large in caliber, showing no evidence of tapering. When present, a PSA usually travels lateral to the femoral head. The PSA vessel is usually described as ectatic; aneurysmal changes, when present, occur at the level of the greater trochanter.¹¹ Turbulent flow secondary to arteriomegaly makes visualization of distal runoff difficult unless appropriately high volumes of contrast and delayed films are used.⁷ The contralateral extremity should also be evaluated, as a PSA has been described as being bilateral in up to 12% of cases.¹¹

Although the case numbers observed are small, the high incidence of complications and the potential for limb loss would seem to warrant prophylactic repair in the asymptomatic patient. In the symptomatic patient, the treatment course is often dictated by the unfolding events. Certain treatment principles have become apparent. In the face of limb-threatening ischemia, distal vessels should be explored before amputation is considered on the basis of poor distal runoff on angiogram. As already stated, unless done properly angiography may miss patent distal vessels. In the presence of aneurysmal changes in the buttock, earlier reports have shown that direct approaches with excision or endoaneurysmorrhaphy and end-to-end interposition grafting can be successful.^{9,11} There are drawbacks to these procedures. The dissection in the gluteal region can be difficult, as the aneurysm sac is often closely adherent to the sciatic nerve. Successfully done, the graft is still exposed to the repeated trauma of daily living as it passes over the extensor surface of the lower extremity. Another option, simple ligation of the aneurysm, would require sufficient collateral circulation via the femoral system.

In more recent cases, efforts have been taken to bypass the PSA, from proximal femoral vessels to distal limb vessels along the flexor aspect of the ex-

tremity. Following bypass, the PSA can be ligated proximally and distally. This may be done at the level of the internal iliac, but as illustrated in this case, sufficient collateral circulation can remain, requiring direct exposure of the aneurysm. Following femoral to distal bypass, percutaneous endovascular obliteration of the aneurysm has also been successfully undertaken, thus avoiding the hazardous gluteal dissection.¹⁴

In conclusion, a persistent sciatic artery is a rare embryologic variant of the lower arterial tree with significant potential morbidity. Knowledge of such an entity may contribute to limb

saving treatment.

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Organ harvesting

TO THE EDITOR: I was very distressed by Dr Irving A. Bunkin's reply to the criticism of his article, "He had a change of heart," by Peter Rogatz, MD.¹⁻² I do not wish to enter into a philosophical discussion concerning the different connotations of "death" and "brain death." I am, however, very disturbed by Dr Bunkin's comment that "the operating room becomes a macabre scene at 2:00 AM." It has been the experience of the staff of my department and the nursing staff in the operating room of this hospital that the harvesting teams are extremely ethical and understanding of the problems presented to an institution where organ harvest is being carried out. I object to the use of the word "extirpated," the primary meaning of which is to "rip out by the roots," although its secondary meaning in Webster's dictionary means surgical removal.

Common usage of the word "extirpation" does not imply delicate surgery and obviously donated kidneys must be extremely carefully dissected and handled with exquisite care to be of use.

New York State law requires that families of deceased persons be approached by medical personnel to solicit organ donation, and letters such as that of Dr Bunkin, when read by the lay public, will certainly not encourage the bereaved to agree to the procedure.

I think it is an editorial responsibility for you to assure that proper disclaimers are made about the sanctity of the operating room used for the procedure, and to try to undo the damage that Dr Bunkin's letter will inevitably do.

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In reply. The opinions expressed in the pages of the *Journal* are those of the authors and do not reflect the editorial

policies of the *Journal*.

PASCAL JAMES IMPERATO, MD
Editor

Perspectives on animal research

TO THE EDITOR: I protest Dr Fred Rosner's biased review of *Perspectives on Animal Research*, vol 1.¹ Rosner is an uncritical defender of animal research,²⁻⁴ and I have written previously that he has falsely characterized the nature of the animal research controversy.⁵ It is, therefore, not surprising that he has written a personal attack rather than a fair, legitimate review of a book that contains many essays critical of animal research.¹

Rosner claims that the publisher, the Medical Research Modernization Committee (MRMC), is "a strong proponent of animal rights." This is false. The MRMC is not an animal rights advocacy group, but a committee interested in serving the public interest by evaluating different medical research modalities with objectivity.

Rosner writes that the MRMC "objects to being called an 'anti-vivisection society' because this term 'does not enjoy a positive connotation.'" Rosner takes his quotations out of context, and not from an MRMC policy statement but from a book review. MRMC objects to being called an antivivisection society because it is not an antivivisection society.

In continuing his *ad hominem* attack, Rosner writes, "All four books were reviewed by animal rights supporters." This too is false. Some of the reviewers are animal rights supporters; others are not. Rosner's failure to criticize the reviews themselves on the basis of poor scholarship or faulty logic suggests that he cannot do so. It is far easier to attempt to undermine the credibility of the reviewers by giving them the label that most guarantees an unfavorable reception by the current medical establishment—"animal rights supporter."

Rosner objects that *Perspectives on Animal Research* is one-sided. The MRMC has solicited papers in defense

of animal research. None has been forthcoming. In any case, Rosner need not fear for the "neutral reader." The medical and scientific literature is already replete with vigorous defenses of animal research, including Rosner's. Many references to such defenses are included in *Perspectives on Animal Research*.

Rather than addressing the soundness of the book's arguments and findings, Rosner discourages reading *Perspectives on Animal Research* on the false grounds that it is an animal rights/antivivisection organ and on the irrelevant grounds that its essays are critical of animal research.

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In reply. I am privileged to serve as Chairman of the Committee on Bioethical Issues of the Medical Society of the State of New York. The committee recently published a major educational report on animal experimentation for medical research¹ which Dr Kaufman cites in his letter. He fails to acknowledge, however, any of the positions taken or arguments presented in that report.

Let me clearly reiterate that members of our committee feel that scientific experiments upon laboratory animals during the course of medical research designed to yield information that might lead to relief of human suffering and/or cure of disease represent a legitimate and moral use of animals for the benefit of mankind. However, pain or discomfort to the animals must be eliminated or minimized by analgesia,

anesthesia, or other means. Animal experimentation is ethically justified if its purpose is to obtain practical benefits to mankind and not simply to satisfy intellectual curiosity. Hunting for sport does not satisfy a legitimate human need and pain inflicted upon animals from hunting is not morally justified.

Medical breakthroughs in diagnosis, treatment, and prevention of heart disease, cancer, diabetes, and many other diseases are directly attributable to the use of animals in research. Such valuable contributions have saved and continue to save lives and relieve human suffering. This support for animal experimentation for medical research in no way conflicts with our strong support for the humane treatment of animals under all circumstances.

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Benzodiazepine controls and the mental health system in New York State

TO THE EDITOR: More than one year has passed since the New York State Department of Health (DOH) imposed, despite considerable opposition from physicians and health care consumers, a regulation requiring that benzodiazepine medications be prescribed through the state's Triplicate Prescription Program. This regulation mandates that benzodiazepines, Schedule IV drugs, be handled in a manner previously reserved for Schedule II medications. In so doing, New York State became the first among all the states to place special burdens on the use of these reasonably safe medications. Much of the reasoning used by the DOH to justify the change of regulation regarding the prescribing of these medications, as set forth in a brochure sent to physicians in February 1988, seemed scientifically questionable to many experts in the field.¹⁻³

In a year in which the budget of the Office of Mental Health (OMH) for state programs and local assistance has been substantially cut, the change in the triplicate prescription program has tangible consequences for the seriously and persistently mentally ill. This is the group identified as most in need of care

in the publicly supported sector of the mental health system. New OMH regulations mandate enhanced Medicaid payments for the care of "designated" patients.⁴ These include, for example, patients discharged from inpatient units within the prior ten days, patients enrolled in the Intensive Care Management program, and those falling into several other categories.

We reviewed patterns of care in our OMH licensed outpatient psychiatric clinic which is a core provider for an inner city community. Discharged patients from inpatient units, including our own, comprise a substantial proportion of patients treated. The clinic has a richer ratio of psychiatric time to total staff time than is the norm among clinics, but even so, psychiatric time remains scarce and waiting time for it can be frustratingly long. The use of benzodiazepines by the clinic psychiatrists was reviewed for one month during the first year of implementation of the new regulations. We found that at least 10% of our clinic's psychiatric time was expended in reevaluating stabilized patients for benzodiazepine renewals during the month studied. These visits occurred in response to regulatory, not clinical, imperatives. Although this finding is derived from only a one-month experience in a single clinic, it does raise serious questions about the possibly detrimental effects of this policy on the public mental health system.

For example, with psychiatric time being a scarce resource in mental health clinics, does this regulation optimize the use made of that time for patients most in need? Who are the patients who are unable to enter the system because clinic appointments are being otherwise utilized? Does the consequent delay in receipt of care lead to costly re-hospitalization? Does the system as a whole serve fewer patients because of inefficient but required expenditures of time? The most fundamental question, then, is, does the DOH's policy inadvertently work at cross purposes and subvert a major policy thrust of the OMH, which is the maintenance in the community of seriously and persistently mentally ill individuals to the extent possible?

In the absence of a move to rescind the regulation, it would seem reasonable, at a minimum, to permit broader use of refill privileges. These are already permitted for several narrowly defined categories of patients and could easily be extended. Permitting wider use of refills would not solve many of

the problems resulting from the implementation of the regulations but would return some degree of necessary prescribing flexibility to physicians. Also, a broadening of the rules governing refills would diminish to some extent the adverse impact of the Triplicate Prescription Program, as applied to the benzodiazepines, on the mental health system. Refill privileges should be extended, at the very least, to OMH operated and licensed clinics, but more properly to all physicians. These limited changes could be accomplished without DOH having to relinquish its enhanced role in policing the prescribing of benzodiazepines in New York State.

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The uniform examination pathway to medical licensure

TO THE EDITOR: One of the most important issues discussed by the American Medical Association (AMA), the Federation of State Medical Boards (FSMB), and the National Boards of Medical Examiners (NBME) has been the development of a Uniform Examination Pathway to Medical Licensure. A uniform pathway has been the object of considerable discussion and debate at the state and national levels for the past two years. This topic was recently discussed at the Annual Meeting of the Federation of State Medical Boards which was held in April 1990 in Birmingham, Alabama.

The Board of Regents' policy to promote access to the professions and to encourage equity in the licensing process made it critically important for New York to participate in this national debate. In 1989, approximately 25% of all foreign medical graduates seeking licensure in the United States did so in New York State. Several legislative leaders, including the late Senator James Donovan, from Utica, NY, have been strong advocates of a uniform examination pathway. Various national organizations, including the Federation

of State Medical Boards, the Association of American Medical Colleges, the American Medical Association, and the Educational Commission for Foreign Medical Graduates have all responded positively to New York State's concern for this approach.

The FSMB, along with a variety of other concerned organizations and groups, has taken an active role in addressing this issue. New York State Education Department staff in the Office of the Professions have participated in many forums with the FSMB and concerned groups to address this issue.

At its January 6, 1989, meeting, the New York State Board for Medicine unanimously passed a resolution endorsing the concept of developing a uni-

form examination pathway to medical licensure. This resolution was later endorsed by the FSMB's Long Range Planning Committee, and at the April 1989 annual meeting of the FSMB, a motion to consider the resolution was introduced and unanimously passed. In September 1989 Parts I and II of NBME became available for the first time to graduates of foreign medical schools. Parts I and II examine students in basic and clinical sciences.

The decision to make available Parts I and II of the NBME to foreign medical graduates is actually only the beginning of a process which should result in a true uniform examination pathway to medical licensure. We anticipate that an entirely new examination sequence

will evolve within the next two to four years. The uniform examination pathway to medical licensure will probably include Parts I and II of NBME as they presently exist and Part III which should serve as a clinical competency component. The projected Part III, however, is yet to be developed, but it is expected that the complete uniform examination sequence will be available in 1994.

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Cancer screening guidelines

In 1990 the New York State Department of Health issued cancer screening guidelines based upon recommendations from the department's Cancer Advisory Panel. The guidelines are intended to aid health care providers in establishing appropriate parameters for screening asymptomatic people. They are not intended to be specific rules or regulations concerning the care of any individual patient.

The department hopes to achieve a reduction in cancer mortality through the early detection of certain cancers such as breast, colon and cervix. Particular cancer sites were chosen because there were adequate scientific data to suggest that early diagnosis would decrease mortality resulting from these cancers. The sites were further narrowed by choosing those cancer types for which there were also adequate scientific data to suggest that screening an asymptomatic population could be done safely, economically and with a high degree of accuracy. Lung cancer is also addressed because of the high prevalence rate associated with this disease. Additionally, the guidelines touch upon ancillary screening of other types and on at-risk populations.

These guidelines are similar, though not identical, to those put forth by the National Cancer Institute and American Cancer Society. They were designed for use in a variety of health care settings commonly found statewide in order to capture the largest part of the population despite divergent socioeconomic aspects of care. These settings include public health clinics, health maintenance organizations, private offices, screening clinics and other types of health care providers. The specific application of the guidelines may vary from one site to another, depending upon the judgment of the individual provider.

Breast Cancer

Breast cancer remains the leading cause of cancer among women in New York State with more than 9,000 new cases diagnosed each year (annual age-adjusted rate of 84 per 100,000). Breast cancer mortality has remained fairly constant over the last two decades while incidence rates have shown a slow but steady increase. Breast cancer accounts for about 4,000 deaths annually in New York State. The New York State Cancer Registry shows breast cancer rates to be highest in densely populated urban areas.

There is little doubt that the stage of this disease at diagnosis remains the most important prognosticator for survival. There are numerous data which relate dimin-

ished survival to an increased primary tumor size and to spread from the primary site to adjacent lymph nodes. Detection of breast cancers at earlier stages (ie, "small" primary tumors with few or no lymph node metastases) improves chances for cure by providing the option to remove the tumor and lymph nodes at the earliest possible time (and lowest stage).

Among the various techniques available for detecting breast masses, the plain-film mammogram stands out as the best screening tool by virtue of rapid execution, a high degree of reliability and low dose of X-ray exposure. While other modalities may offer a higher degree of sensitivity, or greater ease of execution, no other technique provides the combination of attributes that makes mammography the best all-around screening tool presently available.

Colorectal Cancer

There are approximately 12,000 new cases of colorectal cancer diagnosed annually in New York State, and approximately 5,500 deaths per year. It is the second leading cause of cancer mortality in New York State.

The clinical risk factors for colorectal cancer are well known and include ulcerative colitis, familial polyposis, familial cancer syndromes, and the presence of adenomatous polyps.

Once again, survival is largely dependent upon the stage of this disease at the time of diagnosis. Disease confined to the mucosa, or even to the muscularis, confers a good to excellent chance of cure. However, once the malignancy has penetrated the serosa, survival falls off somewhat rapidly.

It is, therefore, the aim of screening techniques for bowel cancer to detect early changes in the mucosa before perpendicular extension through the muscularis occurs. There is a strong sentiment in the medical community that screening is effective, but as yet no screening regimen has been shown unequivocally to be statistically effective in population screening. The department is unable to recommend a particular protocol at this time, but suggests continued use of the screening tools currently employed including digital rectal examination, stool occult-blood testing, sigmoidoscopy and barium enema x-ray examination. Each of these is complementary, providing different kinds of information and exposing patients to varying physical risks. The application of these screening modalities should be determined by the patient and health care provider on an individual basis. Particular attention should be paid to risk factors when planning to screen any given individual.

Cancer of the Uterine Cervix

Cancer of the uterine cervix is less common than breast cancer; however, it still accounts for more than 1,000 cases of invasive cancer each year. The case-fatality ratio of this cancer is analogous to breast cancer in that there is approximately one death for every three newly diagnosed

TABLE 1. Cancer Screening Guidelines for Physicians

Site	Average Patients	At-Risk Patients
Breast	Age 50 and over: annual mammography and clinical examination Ages 40-49: mammography and clinical examination every other year After age 20: monthly breast self-examination Consideration of "baseline" mammography between ages 35 and 39 on the advice of a physician	Patients with any of the following risk factors should have a personalized examination schedule. Previous breast cancer Family history of breast cancer Nulliparity Late first pregnancy Late menopause Fibrocystic breast structure Higher socioeconomic status Jewish
Cervix	Annual Pap smear for all women ages 20-70, and for sexually active women below age 20 When feasible, perform bi-manual pelvic exam along with Pap.	DES exposure Low socioeconomic status Rural dweller
Colon	Perform occult blood testing, sigmoidoscopy and digital rectal examination at regular intervals. (These intervals and the age at which testing should begin are not well-defined; physicians must use their own judgments of individual situations.)	Ulcerative colitis Familial polyposis Adenomatous polyps Family history of cancer (especially colorectal)
Lung Other Sites	No routine screening for lung cancer These guidelines allow for routine evaluation of other organs, such as palpation of the prostate at the time of rectal examination, or of the ovaries and uterus during pelvic examination. However, there are no specific recommendations for other sites at this time.	

cases. There are convincing data from several sources to suggest that both the incidence and mortality from invasive cervical cancer are related to socioeconomic class. The widespread use of the Pap smear is thought to be the reason for the dramatic decline in mortality from this disease over the past three decades. Yet the failure to bring the death rate to zero is thought also to be a failure to bring this common inexpensive technique to all women at risk.

Lung Cancer

Lung cancer is the leading cause of male cancer deaths in New York State each year with almost 6,000 deaths occurring annually. The link to cigarette smoking is well established, and other risk factors are also known. Though survival correlates well with stage of disease at time of diagnosis, lung cancer is only curable one-third of the time in its earliest stage. The screening tools available (chest x-ray, cytology, bronchoscopy) have not been shown to influence mortality in patients diagnosed with lung cancer. Thus, no routine screening for lung cancer is recommended.

Other Cancers

Other cancer sites have not been addressed in these guidelines specifically. However, during the course of other diagnostic examinations there will be ample opportunity to examine body parts potentially at risk, such as skin, ovaries and prostate. These subsequent examinations are considered to be adjuvant benefits of the screening process. Furthermore, as the medical literature concerning screening matures, we expect to acquire new data on cancer screening which may include other sites or modify the recommendations made in this article.

For more information on the screening guidelines, con-

tact the New York State Department of Health, Bureau of Cancer Epidemiology, (518) 474-7950.

Injury mortality in the first year of life

Injuries are the fourth leading cause of death overall both in New York State and nationwide, and the leading cause of death between the ages of one and 44. In New York State children less than one year of age, injuries are the third leading cause of death after perinatal conditions and congenital anomalies. This report focuses on the causes of injury death for children in New York State during the first year of life.

Injury mortality data for the years 1984 through 1988 were obtained from death records of state residents less than one year of age at time of death. Five years of data were used to minimize sampling error. Injury deaths were identified by those death records listing an *International Classification of Diseases*, Ninth Edition (ICD-9) E code in the range E800-E999 as the underlying cause of death. Five deaths due to surgical/medical misadventure or adverse effect of therapeutic drugs were excluded since such causes are not "injury events" in the sense typically used in injury control programs.

There were a total of 343 injury deaths to New York State residents less than one year of age between 1984 and 1988, for an average annual rate of 27.3 deaths per 100,000 residents. Causes of injury death were classified as unintentional, intentional and intention unknown. Unintentional injury deaths were further classified into subcategories reflecting specific cause. The leading causes of injury deaths are listed in Table I. Causes of injury death accounting for less than 3% of the total are pooled in the

TABLE I. Cause of Injury Mortality in Children Less Than One Year of Age in New York State, 1984–1988

Cause of Death	Number of Deaths 1984–1988	Percentage of All Injury Deaths	Annual Rate per 100,000 Residents
Homicide	116	33.8	9.2
Fire	39	11.4	3.1
Suffocation	27	7.9	2.2
Choking: Food	22	6.4	1.8
Motor Vehicle	19	5.5	1.5
Drowning	15	4.4	1.2
Choking: Object	11	3.2	0.9
Other unintentional	23	6.7	1.8
Intention Unknown	71	20.7	5.7
Total Injury Deaths	343	100.0	27.3

“other unintentional” category.

Homicide is the leading cause of injury death in the first year of life, accounting for a third of all injury deaths. The actual proportion may be considerably higher, since a large number of deaths were classified as “intention unknown.” A portion of these infant deaths could be intentional. The proportion of injury deaths due to homicide (34%) are higher than reported for New York State in the early 1980s (24%) by Baker and Waller.¹

The second leading cause of injury death is death from fire. Most of these deaths (72%) were caused by smoke inhalation from fire in a private dwelling. Forms of choking and suffocation also rank high in incidence, collectively accounting for 18% of all injury deaths.

Sex differences in injury mortality rates were examined for all causes of death in the first year of life listed in Table 1. No significant differences were found ($p>0.05$).

The age of death (in months) was examined for all causes of injury death listed in Table I. All deaths were subdivided into thirds of a year (0–3 months, 4–7 months and 8–11 months). The distribution of deaths across age groups was compared to a distribution expected if deaths were proportional across time using a Kolmogorov-Smirnov one sample test. Only deaths from drowning, choking on food and homicide showed significant variation by age at death ($p<0.05$). Figure 1 shows the distribution of percentage of deaths by thirds of a year for these three causes of death. Drownings are most frequent in the last third of

Percentage of Deaths

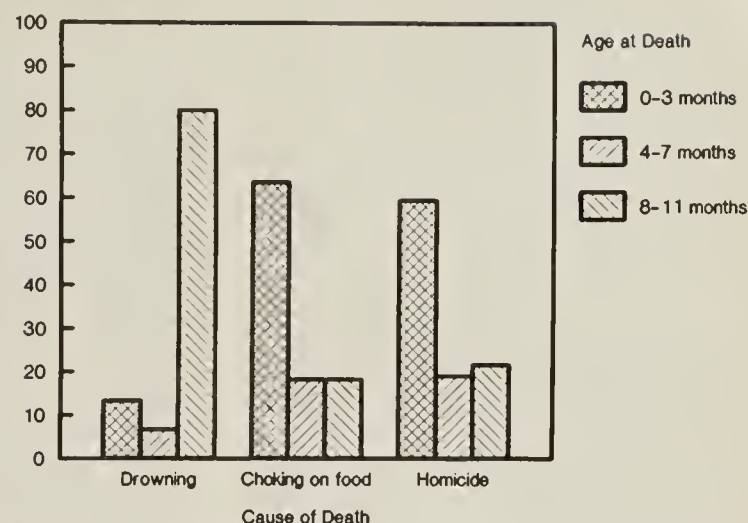


FIGURE 1. Injury mortality in children less than one year of age in New York State, 1984–1988.

the first year of life, which may reflect a tendency to leave older infants unattended in baths and small pools. Choking on food is most frequent during the first four months of life, perhaps having to do with the relative immaturity of newborns. Homicide is also most frequent in the first four months of life. The distribution of deaths by age group shows the need to consider very specific time frames in an individual's life when dealing with injury mortality risk.

A recent report published by the Injury Control Program, New York State Department of Health, *Injury Mortality in New York State 1984–1988*, provides state-wide data on the leading causes of injury death, both unintentional and intentional, with reference to a number of risk factors (for example, sex, age, ethnicity, geography). The report also contains county-specific summaries of injury mortality. For further information contact: Dr John Relethford, Injury Control Program, New York State Department of Health, Corning Tower, Room 621, Empire State Plaza, Albany, NY 12237-0608, (518) 473-1143.

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**THE CRISIS IN HEALTH CARE:
ETHICAL ISSUES**

Edited by Nancy F. McKenzie, PhD.
640 pp. New York, Penguin Books,
1990. \$12.95 (softcover)

This anthology includes 30 essays, on topics as varied as fetal research, Medicaid funding, and sodomy laws. Since 28 of the essays have been previously published, a curious reader might wonder why they have been assembled here. Such a reader would search in vain for a statement from the editor explaining the choice of topics, authors, and positions. Looking for such an explanation in the foreword, the reader would find instead a beautifully written essay on a familiar topic, the dehumanizing effects of medical training, which is virtually unrelated to the rest of the book.

However, the anthology's double title may give the reader an approach to understanding the organization of its contents: about half the essays concern a crisis in health care, specifically an economic one, and the other half concern a variety of largely unrelated ethical issues. The question then becomes why these papers on diverse ethical topics are interspersed with an otherwise coherent group of papers on economic and social issues. The purpose could hardly be to present a survey of the most important topics in medical ethics, since relatively small issues are discussed extensively, while obviously large issues, such as abortion, are entirely absent. Nor could the goal be to present the most important developments in current ethical discourse, since many of the papers are dated (some more than 20 years old), and deserve consideration as classics rather than as illustrations of modern thinking.

However, one can gather some sense of the editor's motivation by reading her own two essays, which are the only ones in the book not previously published. Here one finds articulated, in a polemical but effective fashion, a two-part argument. The first is that the American medical system has been in a state of crisis for a long time, that AIDS and other current problems are simply unmasking the crisis, that the crisis involves primarily the unavailability of health care for the poor, and that all this is the result of the callous attitudes and discrimination which are entrenched in American society and par-

ticularly in the medical profession. The second is that this crisis constitutes an ethical crisis for physicians, since they have the power to change these inequities and therefore a moral obligation to do so. I can only assume that the papers on various ethical topics were included to bolster this latter point, that the economic and social crisis in medicine is best understood as an ethical problem.

No thoughtful observer would dispute the contention that we have a social and economic crisis in medicine, though one might disagree about the sources of the problem. However, the most interesting part of the argument concerns the proposition that these are ethical issues. The editor holds that traditional "client-centered ethics" is no longer sufficient, since recent developments, especially the rise of medicine as a "corporate enterprise," call for a new ethics of institutions: "The evolved crisis in health care shows us that caretakers must begin to acknowledge that they are as responsible for the quality of the institutions of which they are agents as for their patient-centered action" (p 121).

If the point of the book, then, is to advance this thesis, how well does it do? In some ways, very well. The papers on economic issues are almost all either very good or very important, and a few are both. They include surveys of the availability and use of medical care, ethical discourses on the right to health care and on conflicts in managed care systems, and editorials on important new directions for the health care system. Taken together, these papers present a ringing and convincing case that a crisis exists and demands attention, even if they offer only the familiar solutions of restructuring systems and infusing vast amounts of money. The papers on other ethical issues, while unrelated to each other and to the rest of the volume, are individually quite good; they are thoughtful, balanced, and sophisticated discussions by leading thinkers in the field.

The editor makes no effort to hide her hostility toward the medical profession, but this hostility is based on a curious and disputable estimate of the profession's power. In her reckoning, it is ultimately callous self-interest on the part of the medical establishment that has brought about the current crisis, by turning medicine into a corporate enterprise designed to make money for

physicians by serving the wealthy and ignoring the needs of the poor and powerless. Furthermore, she holds, since the medical profession is so powerful, it alone could reverse the ills of society, by throwing its weight behind various proposals, not only for changes in health care delivery, but also for improved housing and protection against discrimination.

Convincing or not, these arguments are not, properly speaking, "ethical" discourse. The papers written by genuine ethicists in this volume demonstrate the characteristic that makes ethical arguments fascinating: they weigh one good against another, and thus require painful choices, as in the debate about the symbolic value of respect for dead bodies versus the practical value of making organs available for transplantation. The arguments about the causes and remedies of the crisis in health care, as presented here, involve no such calculus of competing goods. Instead, they pit the good of equal access to care against the evil of corporate medical greed. When you think there is some good on your opponent's side, you have an ethical argument, and an interesting one. When you are certain that your opponent is evil, you have a moral argument, and perhaps a compelling one, but not a very interesting one.

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**AGENCY UNDER STRESS: THE SOCIAL
SECURITY ADMINISTRATION IN
AMERICAN GOVERNMENT**

By Martha Derthick. 231 pp. Washington, DC, The Brookings Institution, 1990. \$32.95 (clothcover)

Many Americans believe that anything the government does can be done better and more efficiently by private industry. Derthick demonstrates the wisdom of this assumption in an examination of two programs administered by the huge Social Security Administration (SSA) bureaucracy. In 1974 the SSA implemented the supplemental security income (SSI) program supporting needy blind, aged, and disabled people. What were the outcomes? About \$400 million was spent in error in the program's first year: 13.3% were over-

paid; 5.4% were underpaid; 6.1% were ineligible persons; field employees worked 1.86 million overtime hours in one quarter in 1974—75 times the usual amount; computer systems were not ready; and obviously other SSA programs suffered.

In the 1980s, Congress ordered the SSA to review the eligibility of disability insurance recipients. More than 1.2 million cases were reviewed and almost 500,000 people had their benefits terminated. About 75% of the recipients inundated the courts with appeals and the judges overwhelmingly (about 65%) ruled against the SSA.

Based on her analysis of these two examples, Derthick comments: "The pathologies of bureaucracy itself are found to be at fault." In essence, Derthick argues that public policymaking does not concern itself with providing guidance for effective administration. When guidance is given, it is usually not conducive to good administration. In our democratic system, the bureaucrats receive conflicting cues from the president, the Congress, and/or the courts.

As I pondered why Derthick's book would be of any interest to physicians, I was frankly at a loss. This book is replete with numerous footnotes and is not leisure reading. Then, the thought came to me that her two case studies of the huge bureaucracy of the federal government's SSA does provide ammunition for those who oppose governmental interference with the practice of medicine. In both illustrations, the SSA experienced colossal disasters.

Certainly, those who oppose national health insurance or any variation of "socialized medicine" will find appropriate expert quotes to emulate Cassandra's calamitous predictions in their arguments. Critics will relish the data indicating that bureaucrats cannot carry out the intent of the legislation with fidelity to the stated purpose.

On the other hand, those who are concerned with the rapidly burgeoning "managed care" health care delivery systems may find lessons. Policymakers should also be absorbed with the day-to-day details. "Persons who presumably would give painstaking attention to instructions on how to use a pasta machine or a piece of video equipment make major policy decisions with virtually no thought to whether a complex organization of human beings can reasonably be expected to execute their commands."

Perhaps the situation is unresolvable in a democracy containing a constitu-

tional system of checks and balances. Often, the result is constant changes in the elected official, in the appointed bureaucrats, in the law, in the extent of the paperwork required to negotiate the health care delivery system, and in the administration of programs. Considering all these aspects, Derthick evokes the quote of James Madison about the changeable policy that "poisons the blessing of liberty itself":

It will be of little avail to the people, that the laws are made by men of their own choice, if the laws be so voluminous that they cannot be read, or so incoherent that they cannot be understood; if they be repealed or revised before they are promulgated, or undergo such incessant changes that no man, who knows what the law is today, can guess what it will be tomorrow. Law is defined to be a rule of action; but how can that be a rule, which is little known, and less fixed?

What does Derthick suggest as a remedy? She aims to provide policymakers with information about the capability of the bureaucratic agencies to implement mandated activities. Derthick recommends the preparation of "State of the Agency" reports that would detail administrative ability to put into practice the policies set by the president, the Congress, and the courts. With this information, policymakers from any of the competing jurisdictions could at least consider the ramifications of their executive orders, their legislation, or their judicial decisions. These reports are to be compiled by staff agencies of Congress such as the Congressional Research Service, Congressional Budget Office, General Accounting Office, and Office of Technology Assessment.

Medical policymakers, administrators, and historians will be among those most rewarded by reading this well-documented and analytical book.

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RESOLVING RESISTANCES IN PSYCHOTHERAPY

By Herbert S. Strean, DSW. 312 pp. New York, Brunner/Mazel Publishers, 1990. \$22.95 (softcover)

This monograph is a refreshing and welcome addition to the plethora of material available to the psychotherapist

learning his or her craft. Dr Strean, a well-known author, clinician, and teacher of psychoanalytic psychotherapy, conceives of psychotherapy as the process of the therapist helping the patient to overcome the inevitable roadblocks that develop in their interaction. Resistance, rather than something to be avoided, is, in fact, necessary and integral to useful therapy.

The first portion of the book is a historical overview of resistance in therapy. First, the concept of resistance itself is explored from the points of view of numerous theoreticians, including Freudians, neo-Freudians, and non-Freudians. This chapter is followed by a similar overview of these and other authors' thoughts on the role of the therapist in overcoming resistance. Dr Strean is very thorough in presenting the essential theory of at least 25 contributors. Such an overview, though, is necessarily theoretical and far removed from the practicalities of psychotherapeutic practice.

The second portion of the book comes to life. Here, Dr Strean uses many clinical examples to illustrate the various shapes and forms that resistance takes throughout the stages of therapy. The stages are divided as follows: "On Beginning the Treatment: Initial Resistances"; "The First Treatment Crisis: Wishes to Flee Treatment and other Impasses"; "The Middle Phase: Refusals to Comply with Basic Requests"; "The Middle Phase Continued: Subtle Resistances"; "Termination: The Pain of Separation." The reader learns to recognize and conceptualize resistance in the first phone call the patient makes to the therapist in the last weeks of their therapeutic relationship.

The importance of Dr Strean's book is in how successfully he handles the clinical vignettes. Each case begins with a concise statement of who the therapist and patient are, why the patient is seeking treatment, and often where the treatment is taking place such as a college counseling center or a mental hygiene clinic. This serves to personalize the case and involve the reader in the process. And Dr Strean's care in what would seem to be the trivial matter of naming the patient and therapist is appreciated. We get to know Sally C., Harvey M., and therapists Ms E., Dr M., and Mr Q., not patients A, B, and C and Drs X, Y, and Z.

There is another unique aspect of Dr Strean's use of clinical material. He presents cases where either incorrect management or lack of recognition of

resistance leads to the patient's exiting from therapy. Dr Strean then presents follow-up where the same patient begins treatment with another therapist who manages resistance successfully. There is likely no better way to teach how to "do therapy," in book form, than such a presentation of others' trials and errors.

This reviewer was troubled by one aspect of Dr Strean's presentation. He advocates treating the emergence of a moderate to severe depression purely psychotherapeutically. He suggests that the prescription of medication may in fact be counter-productive. Such a recommendation is not in line with modern clinical practice. There is no reason why medication should not be considered to help alleviate the symptoms of clinical depression. The transference aspects of prescription must, though, become part of the therapy. Our differences in this area likely result from professional bias as Dr Strean holds a doctorate in social work.

Resolving Resistance in Psychotherapy will likely be added to the list of practical works that will be recommended to the beginning therapist. All psychotherapists will appreciate Dr Strean's effective demonstration that the resolution of resistance is the essence of psychotherapy.

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GERIATRIC NUTRITION: A COMPREHENSIVE REVIEW

Edited by John E. Morley, MB, Zvi Glick, PhD, and Laurence Z. Rubenstein, MD. 521 pp, illustrated. New York, Raven Press, 1990. \$89.00 (hardcover)

In the past, geriatric medicine and nutrition science have struggled to gain their deserved recognition in the practice of internal medicine. A growing body of knowledge has developed from studying nutrition in relation to aging and care of the geriatric patient. *Geriatric Nutrition: A Comprehensive Review* provides an extensive review of the current literature on this expanding and fascinating area of research and clinical practice. In the editors' own words, this book emphasizes "how age-associated ages in physiology and function influence nutritional status, and how nutrition may influence aging and age-asso-

ciated morbidity."

The editors are well known for their expertise in geriatrics. Dr Morley has written numerous chapters and journal articles on geriatric nutrition. Well-chosen authors of the individual chapters discuss the many facets of the subject in this text, which is divided into four sections: "Nutrition and Aging," "Nutritional Deficiencies," "Systems Malfunction and Nutrition," and "Special Topics in Geriatric Nutrition." The first section opens with introductory chapters on the demographics, epidemiology, and health services of the aging population, molecular theories of aging, and views on nutrition and longevity. These are followed by discussions of age-related changes in energy metabolism and nutritional requirements of the elderly regarding protein, fat, carbohydrates, vitamins, and minerals. Studies on these nutrient intakes are compared to the recommended dietary allowances (RDA), which categorized all individuals older than age 51 under one heading before 1989. Limited data on the elderly did not greatly alter the new RDAs. The section concludes with methods in nutritional assessment that use anthropometry and biochemical indices, and preventive aspects of nutrition in age-related disease.

The second section, "Nutritional Deficiencies," reviews the assessment and treatment of various deficiency states, including protein-energy malnutrition (to which the elderly are particularly susceptible) and vitamin and mineral disorders. Individual vitamins and minerals are discussed in terms of function and toxicity, the latter due to a high prevalence of megavitamin use in this population. Chapters are presented on the metabolic aspects of calcium and vitamin D, zinc, water, and the nutritional anemias.

"Systems Malfunction and Nutrition" covers the implications of aging and nutrition on immune status, and also gastrointestinal functioning, including the oral cavity and the liver. Certain disease states affected by these factors are reviewed, such as diabetes mellitus, cardiovascular diseases, cancer, and obesity.

The fourth section, dealing with special topics, focuses on important subjects that have gained increasing attention due to their uniqueness. The discussion of malnutrition in the nursing home emphasizes its alarmingly high prevalence and need for intervention. Techniques in nutritional support of the elderly, pressure sores, food-

drug/drug-food interactions, interdisciplinary nutrition teams, and ethical and legal aspects of providing food and water are a few of the pertinent topics presented.

Each well-referenced chapter is clearly and concisely written. Tables and figures are effectively used throughout the text for clarification or summarization. One aspect that may be frustrating to the reader, however, is the repetition of information within some of the separate but related chapters. For example, nutritional assessment is discussed in each of the first three chapters: general nutritional assessment in the first section, assessment for protein-energy malnutrition in the second, and assessment for obesity in the third. Combining the closely related discussions would have avoided repetition and the different recommendations, for example in the use of body weight-height reference tables and body mass index to assist in determining a patient's appropriate weight status. The lack of standards for the simple measurement of body weight only exemplifies the great need for continued research in all aspects of geriatric nutrition.

In addition, the chapter on memory enhancement in mice appears out of place in a text of this nature. The nutritional problems of cognitively impaired elderly, with reference to studies on memory, might have been more relevant. A chapter devoted to clinical and research methods in the dietary assessment of the elderly might have been useful, as well.

Yet overall, this text is an excellent and unique addition to the developing subspecialty of geriatric medicine. As the preface notes, it provides a "systematic and comprehensive coverage of geriatric nutrition." It is highly recommended for both researchers and clinicians involved in studying and caring for our elderly and aging populations.

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TUBAL RECONSTRUCTIVE SURGERY

By Ginter Sotrel, MD. 281 pp, illustrated. Philadelphia, Lea & Febiger, 1990. \$75.00 (hardcover)

The text of this volume is carefully

organized and the subject of tubal reconstructive surgery is thoroughly covered. The contents are divided into three parts. The first section reviews tubal anatomy and physiology and pathologic conditions encountered by the gynecologist in the management of infertility caused by tubal abnormalities. The methods for preoperative assessment and preparation of the patient are included in the initial 97 pages. The chapters on microsurgical instruments and the prevention of postoperative adhesions are nicely structured so that the student and experienced reproductive surgeon can gain much information by careful perusal.

The second section, which constitutes the major part of the book, covers specific tuboplastic procedures for proximal, midsegment, and distal obstructions. The author devotes more text to the use of tubouterine implantation rather than tubocornual anastomosis for proximal obstruction although the current trend is for the latter procedure. The use of lacrimal probes to test patency of segments is illustrated and described in several drawings. However, this maneuver is fraught with the danger of endosalpingeal trauma. Retrograde chromopertubation is the preferred technique. Many of the illustrations show a serosal circumcission type of incision, but this reviewer cannot find any benefit from such a procedure.

The final section describes ancillary procedures occasionally used in conjunction with tubal surgery such as uterine suspension, ovarian resection, and myomectomy. One of the chapters describes therapeutic or operative laparoscopy and hysteroscopy.

Minor criticisms include the lack of magnifications for the photomicrographs, the use of the word "dye" rather than "contrast material" for hysterosalpingograms (HSGs), and the term "cautery" for electrosurgical procedures such as coagulation and cutting. Unfortunately, laparoscopic illustra-

tions lose their effectiveness in black and white reproductions.

Notwithstanding these criticisms, this book is a fine addition to the texts that deal with tuboplasty, and offers the gynecologist a well-referenced and profusely illustrated work on the subject.

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SUCCESSFUL MODELS OF COMMUNITY LONG TERM CARE SERVICES FOR THE ELDERLY

Edited by Eloise H. P. Killeffer, EDM,
and Ruth Bennett, PhD. 174 pp. Binghamton, NY, The Haworth Press,
1990. \$24.95 (hardcover)

This book consists of the proceedings of a conference entitled "Successful Models of Community-Based, Long Term Care for the Elderly," held at Columbia University School of Public Health in November 1987, with sponsorship by the then new Division of Geriatrics and Gerontology. It was an effort to bring together administrators and clinicians of community geriatric programs to share new ideas and discuss existing models that were functioning at the time of the conference.

The presenters at this conference were from programs that had a mix of public and private resources that provided long term care to older adults in the home setting. All programs were financially sound and there was a mix of both urban and rural settings. All the presenters were recognized leaders in the field of administration, education, and health care delivery in the geriatric field.

Eloise H. P. Killeffer, EDM, is a senior research scientist at Columbia University Center for Geriatrics and Gerontology and the Practicum Coordinator for this division. Her co-editor,

Ruth Bennett, PhD, is Director of Graduate Education of the Division of Geriatrics and Gerontology at Columbia University School of Public Health. Both editors have written numerous articles in these areas.

The book is organized into three sections: models of community-based programs, educational aspects of teaching in this area, and policy development on long term care. Each section is well organized and each presenter covers different aspects of each topic area. The book has a listing of references utilized by each presenter as well as a section of recommended readings.

This book will have a very limited audience and probably will have little appeal for physicians unless they are involved in administration. Since the time of this conference many changes have occurred in the health care financing of these long term care programs. Unfortunately, in some cases, these have been to the detriment of the recipients of service. Many of the same principles apply today and there are many innovative ideas presented by the authors that could be implemented in our current health care environment. No mention is made by the editors of the current status of these programs, but it would be of interest to have the same programs reviewed today to see how their scope of services has changed.

The two sections on education and policy development have relevance today as medical schools and residency programs include more emphasis on geriatric education and courses on political and policy decision making. For the geriatric educator the sections on the practicum model of education will be of interest.

This book is well produced and organized. As stated above, it will be of interest to those clinicians who work in this area of program development and education.

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BOOKS RECEIVED

AIDS

Preventing AIDS: The Design of Effective Programs. Edited by Ronald O. Valdiserri, MD. 304 pp, illustrated. New Brunswick, NJ, Rutgers University Press, 1989. \$15.00 (softcover)

The AIDS Disaster: The Failure of Organizations in New York and the Nation. By Charles Perrow and Mauro F. Guillen, PhD. 206 pp. New Haven, Conn, Yale University Press, 1990. \$25.00 (clothcover)

Advances In Chemotherapy of AIDS. Edited by Robert B. Diasio, MD, and Jean-Pierre Sommadossi, PhD. 111 pp, illustrated. Elmsford, NY, Pergamon Press, 1990. \$39.50 (hardcover)

BIOCHEMISTRY

Harper's Biochemistry. Twenty-Second Edition. By Robert K. Murray, MD, Daryl K. Granner, MD, Peter A. Mayes, PhD, and Victor W. Rodwell, PhD. 693 pp, illustrated. East Norwalk, Conn, Appleton & Lange, 1990. \$29.50 (paperback)

DERMATOLOGY

Dermatology. First Edition. Edited by Milton Orkin, MD, Howard I. Maibach, MD, Mark V. Dahl, MD. 677 pp, illustrated. East Norwalk, Conn, Appleton & Lange, 1991. \$37.95 (softcover)

DRUG ABUSE

Drugs in Hispanic Communities. Edited by Ronald Glick and Joan Moore. 275 pp. New Brunswick, NJ, Rutgers University Press, 1990. \$14.00 (softcover) (clothcover \$37.00)

ENDOCRINOLOGY

Progress In Endocrine Research and Therapy. Volume 5. ACTH, Cushing's Syndrome and Other Hypercortisolemic States. Edited by Dieter K. Ludecke, MD, George P. Chrousos, MD, and George Tolis, MD. 336 pp, illustrated. New York, Raven Press, 1990. \$95.00 (hardcover)

GASTROENTEROLOGY

Year Book of Digestive Diseases 1990. Edited by Norton J. Greenberger, MD, and Frank G. Moody, MD. 454 pp, illustrated. Chicago, Mosby Year Book, Inc, 1990. \$57.95 (hardcover)

Irritable Bowel Syndrome: One Disease, Several, or None? (Perspectives In Digestive Disease Series, Vol. 5). Edited by G. Bianchi Porro and N. W. Read. 82 pp, illustrated. New York, Raven Press, 1990. \$38.00 (hardcover)

Pathogenesis of Functional Bowel Disease. Edited by William J. Snape, Jr, MD. 368 pp, illustrated. New York, Plenum Medical Book Co, 1989. \$65.00 (hardcover)

Textbook of Secretory Diarrhea. Edited by Emanuel Lebenthal, MD, and Michael E. Duffy,

MD. 456 pp, illustrated. New York, Raven Press, 1990. \$110.00 (hardcover)

GERIATRICS

Successful Models of Community Long Term Care Services for the Elderly. Edited by Eloise H. P. Killeffer, EdM, and Ruth Bennett, PhD. 174 pp. Binghamton, NY, The Haworth Press, 1990. \$24.95 (hardcover)

Diabetes Mellitus in the Elderly: A Practical Guide. Edited by Steven R. Gamberg, MD. 288 pp, illustrated. New York, Raven Press, 1990. \$69.00 (hardcover)

Choosing a Nursing Home. By Seth B. Goldsmith, PhD. 267 pp. New York, Prentice Hall Press, 1990. \$10.95 (softcover)

HEALTH CARE ADMINISTRATION

Agency Under Stress. The Social Security Administration In American Government. By Martha Derthick. 231 pp. Washington, DC, The Brookings Institution, 1990. \$32.95 (clothcover)

HISTORY OF MEDICINE

Health Care in the Parisian Countryside, 1880-1914. by Evelyn Bernette Ackerman. 258 pp, illustrated. New Brunswick, NJ, Rutgers University Press, 1990. \$45.00 (clothcover)

INFECTIOUS DISEASES

Infectious Diseases of the Female Genital Tract. Second Edition. By Richard L. Sweet, MD, and Ronald S. Gibbs, MD. 494 pp, illustrated. Baltimore, Md, Williams & Wilkins, 1990. \$68.00 (hardcover)

INTERNAL MEDICINE

Cerebrovascular Disorders. Fourth Edition. By James F. Toole, MD. 567 pp, illustrated. New York, Raven Press, 1990. \$95.00 (hardcover)

Atherosclerosis Reviews: Prevention and Non-invasive Therapy of Atherosclerosis. Volume 21. Edited by Alexander Leaf, MD, and Peter C. Weber, MD. 220 pp, illustrated. New York, Raven Press, 1990. \$69.00 (hardcover)

The ICU Book. By Paul L. Marino, MD. 713 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$39.50 (paperback)

Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy. Edited by Stephen Falk, MD. 670 pp, illustrated. New York, Raven Press, 1990. \$125.00 (hardcover)

Venous Thromboembolic Disorders. Edited by Jacques R. Leclerc, MD. 448 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$69.50 (hardcover)

LABORATORY MEDICINE

Manual of Laboratory Immunology. Second

Edition. By Linda E. Miller, PhD, Harry R. Ludke, BS, Julia E. Peacock, MS, and Russell H. Tomar, MD. 427 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$39.50 (paperback)

MEDICAL HISTORY

Alton Ochsner, Surgeon of the South. By John Wilds and Ira Harkey. 268 pp, illustrated. Baton Rouge, La, Louisiana State University Press, 1990. \$24.95 (hardcover)

MICROBIOLOGY

Medical Microbiology Synopsis. By Donald M. McLean, MD, and John A. Smith, MD. 305 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$28.50 (paperback)

MISCELLANEOUS

The High Blood Pressure Relief Diet: The Easy Lifetime Nutrition Plan That Helps. By Dr James Scala. 324 pp. New York, Penguin Books, 1990. \$9.95 (paperback)

Practical Medical Halachah. Third Revised Edition. By Fred Rosner, MD, and Harav Moshe Tendler, PhD. 191 pp. Hoboken, NJ, KTAV Publishing House, Inc, 1990. \$18.95 (hardcover)

Beyond Dieting: Psychoeducational Interventions for Chronically Obese Women: A Non-Dieting Approach. By Donna Ciliska, RN. 192 pp, illustrated. New York, Brunner/Mazel, 1990. \$25.00 (hardcover)

Natural Medicine for Children. By Julian Scott, PhD. 191 pp, illustrated. New York, William Morrow & Co, Inc, 1990. \$24.95 (clothcover)

Being Human: The Art of Feeling Alive. By Haskell E. Bernstein, MD. 220 pp. New York, Gardner Press, Inc, 1990. \$14.95 (paperback)

Marriage: The Phoenix Contract. By Dale D. Cornell, MD, and Frances Gay Ericson, MA. 165 pp. St Louis, Mo, Warren H. Green, Inc, 1990. \$22.50 (paperback)

The Celebrity Phone Book. By Scott Siegel and Barbara Siegel. 320 pp. New York, Plume, 1990. \$9.95 (paperback)

Groups in Health Care Settings. Edited by Janice H. Schopler, PhD, and Maeda J. Galinsky, PhD. 184 pp. Binghamton, NY, The Haworth Press, Inc, 1990. \$29.95 (hardcover)

Human Sex Determination: An Historical Review and Synthesis. By Dr. Ron Wells. 244 pp. Tharwa, Australia, Riverlea Publications, 1990. \$30.00 (softcover)

Understanding the Nursing Process. Fundamentals of Care Planning. Fourth Edition. By Leslie D. Atkinson, RN, and Mary Ellen Murray, RN. 146 pp, illustrated. Elmsford, NY, Pergamon Press, Inc, 1990. \$19.95 (softcover)

Journey to Brotherhood: Awakening, Healing and Connecting Men's Hearts. By Frank D. Cardelle, PhD. 299 pp. New York, Gardner Press,

1990. \$15.95 (softcover)

A Systemic Harpoon into Family Games: Preventive Interventions in Therapy. By Giuliana Prata, MD. 192 pp. New York, Brunner/Mazel Publishers, 1990. \$25.00 (hardcover).

Illustrated Book of Pregnancy & Baby Care. By Good Housekeeping. 256 pp, illustrated. New York, William Morrow & Co, Inc, 1990. \$22.95 (clothcover).

Alternative In Healing: An Open-Minded Approach to Finding the Best Treatment for Your Health Problems. By Simon Mills, MS, and Steven J. Finando, PhD. 240 pp, illustrated. New York, Nal Penguin, Inc, 1989. \$12.95 (softcover)

The Feeling Good Handbook. By David D. Burns, MD. 587 pp. New York, Penguin Books, Inc, 1989. \$10.95 (softcover)

Mayo Clinic Family Health Book. By The Mayo Clinic. 1,396 pp, illustrated. New York, William Morrow & Co, Inc, 1990. \$34.95 (clothcover)

Successful Private Practice in the 1990s. A New Guide for the Mental Health Professional. By Joan Kaye Beigel, MEd, Ralph H. Earle, PhD. 224 pp. New York, Brunner/Mazel Publishers, 1990. \$21.95 (softcover)

Freud and Moses: The Long Journey Home. By Emanuel Rice, MD. 266 pp. Albany, State University of New York Press, 1990. \$49.50 (hardcover)

The Medical Entrepreneur's Handbook. Edited by Harvey E. Knoernschild, MD. 214 pp. San Jose, Calif, CE/Q Publishers, Inc, 1990. \$24.00 (softcover)

Effective Supervision: A Task-Oriented Model for the Mental Health Professions. By D. Eugene Mead, EdD. 192 pp. New York, Brunner/Mazel Publishers, 1990. \$22.50 (hardcover)

PDR Indications Index: Edition 44-1990. Edited by Mukesh Mehta, RPH. 350 pp. Oradell, NJ, Medical Economics Books, 1990. \$19.95 (softcover)

A Guide to Family Centered Circle Drawings. By Robert C. Burns, PhD. 224 pp, illustrated. New York, Brunner/Mazel Publishers, 1990. \$23.95 (hardcover)

Psychological Trauma and the Adult Survivor: Theory, Therapy, and Transformation. By I. Lisa McCann, PhD, and Laurie Anne Pearlman, PhD. 376 pp. New York, Brunner/Mazel Publishers, 1990. \$39.95 (hardcover)

NEUROLOGY

Synopsis of Neurology. By Richard Lechtenberg, MD. 173 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$19.75 (paperback)

Textbook of Child Neurology. Fourth Edition. By John Menkes, MD. 825 pp, illustrated. Malvern, Pa, Lea & Febiger, 1990. \$78.00 (hardcover)

Current Practice of Clinical Electroencephalography. Second Edition. Edited by David D. Daly, MD, and Timothy A. Pedley, MD. 844 pp, illustrated. New York, Raven Press, 1990. \$85.00 (hardcover)

Advances in Neurology. Parkinson's Disease: Anatomy, Pathology, and Therapy. Volume 53. Edited by Max B. Streifler, MD, Amos D. Korczyn, MD, Eldad Melamed, MD, and Moussa B. H. Youdin, PhD. 596 pp, illustrated. New York, Raven Press, 1990. \$125.00 (hardcover)

OBSTETRICS AND GYNECOLOGY

Diagnosis and Treatment of Extrauterine Pregnancies. By Nicholas Kadar, MD. 256 pp, illustrated. New York, Raven Press, 1990. \$78.00 (hardcover)

Manual of Gynecologic Oncology and Gynecology. Edited by M. Steven Piver, MD. 416 pp, illustrated. Boston, Mass, Little Brown & Co, 1989. \$22.50 (spiralbound)

Gynecology for the House Officer. Edited by Stephen H. Cruikshank, MD, and Allan Chamberlain, MD. 211 pp, illustrated. Baltimore, Md, William & Wilkins, 1990. \$17.95 (softcover)

Contraception: The Facts. By Peter Bromwich and Tony Parsons. 218 pp. Cary, NC, Oxford University Press, 1990. \$21.95 (hardcover)

ONCOLOGY

Neoplasms with Eccrine Differentiation. By Pascual Abenoza, MD, and A. Bernard Ackerman, MD. 536 pp, illustrated. Malvern, Pa, Lea & Febiger, 1990. \$120.00 (hardcover)

OPHTHALMOLOGY

Clinical Tests of Vision. By Lars Frisen, MD. 222 pp, illustrated. New York, Raven Press, 1990. \$59.00 (softcover)

ORTHOPEDIC SURGERY

Reconstruction of the Child's Hand. Edited by Peter R. Carter, MD. 321 pp, illustrated. Malvern, Pa, Lea & Febiger, 1990. \$75.00 (hardcover)

OTOLARYNGOLOGY

Handbook of Vertigo. By Michael E. Glasscock III, MD, Roberto A. Cueva, MD, Britt A. Thedinger, MD. 122 pp, illustrated. New York, Raven Press, 1990. \$49.00 (clothcover)

PEDIATRICS

Principles and Practice of Pediatrics. Edited by Frank A. Oski, MD, Catherine D. DeAngelis, MD, Ralph D. Feigin, MD, Joseph B. Warshaw, MD. 2,000 pp, illustrated. Philadelphia, J. B. Lippincott Co, 1990. \$99.50 (hardcover)

Neonatal Seizures. Edited by Claude G. Wasterlain, MD, and Paul Vert, MD. 336 pp, illustrated. New York, Raven Press, 1990. \$98.00 (hardcover)

PHARMACOLOGY

Cardiovascular Pharmacology. Third Edition.

Edited by Michael J. Antonaccio, PhD. 572 pp, illustrated. New York, Raven Press, 1990. \$75.00 (hardcover)

Goodman and Gilman's: The Pharmacological Basis of Therapeutics. Eighth Edition. Edited by Alfred Goodman Gilman, MD, Theodore W. Rall, PhD, Alan S. Nies, MD, and Palmer Taylor, PhD. 1,811 pp, illustrated. Elmsford, NY, Pergamon Press, Inc, 1990. \$79.50 (hardcover)

PSYCHIATRY

Hallucinations in Clinical Psychiatry: A Guide for Mental Health Professionals. By Ghazi Asaad, MD. 160 pp. New York, Brunner/Mazel Publishers, 1990. \$21.95 (hardcover)

Clinical Hypnosis & Therapeutic Suggestions in Patient Care. Edited by Rothlyn P. Zahourek, MS. 272 pp, illustrated. New York, Brunner/Mazel Publishers, 1990. \$25.00 (paperback)

A Casebook in Psychiatric Ethics. Formulated by the Committee on Medical Education. By the Group for the Advancement of Psychiatry. 128 pp. New York, Brunner/Mazel Publishers, 1990. \$14.95 (paperback)

Breaking the Silence: Art Therapy with Children from Violent Homes. By Cathy Malchiodo, MA. 228 pp, illustrated. New York, Brunner/Mazel Publishers, 1990. \$29.95 (hardcover)

Psychoanalytic Approaches to Supervision (Current Issues in Psychoanalytic Practice: Monographs of the Society for Psychoanalytic Training, Number 2). Edited by Robert C. Lane, PhD. 224 pp. New York, Brunner/Mazel, 1990. \$25.00 (hardcover)

RADIOLOGY

Pocket Atlas of Normal CT Anatomy of the Head and Brain. By Anton N. Hasso, MD, and Miyuki Shakudo, MD. 85 pp, illustrated. New York, Raven Press, 1990. \$14.95 (paperback)

RHEUMATOLOGY

Anti-Rheumatic Drugs. Edited by M. Orme, 241 pp, illustrated. Elmsford, NY, Pergamon Press, Inc, 1990. \$67.50 (hardcover)

SURGERY

Current Practice of Surgical Stapling. Edited by Mark M. Ravitch, MD, Felicien M. Steichen, MD, and Roger Welter, MD. 324 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$79.50 (hardcover)

Bowel Obstruction: Differential Diagnosis and Clinical Management. By John P. Welch, MD. 736 pp, illustrated. Philadelphia, W. B. Saunders Co, 1990. \$95.00 (hardcover)

UROLOGY

Treatment Perspectives in Urologic Oncology. Edited by Richard D. Williams, MD, and Peter R. Carroll, MD. 240 pp, illustrated. Elmsford, NY, Pergamon Press, Inc, 1990. \$47.50 (hardcover)

Inhalation of volatile compounds reported among teenagers

Similar to the "high" achieved by sniffing propellants from aerosol cans, which gained attention in the 1970s, there are increasing reports of teenagers getting "high" by inhaling butane and propane, with sometimes fatal results. Siegel and Wason reported on two teenage boys who died as a result of inhaling these volatile compounds (*N Engl J Med* 1990; 323:1638).

In the first case, an 11-year-old boy who had collapsed in the bathroom of a movie theater was found to have a container of cigarette lighter fuel and a plastic bag, as well as several bottles of typewriter correction fluid in his pocket. The postmortem toxicologic analysis detected butane in the boy's blood and lung tissue.

A 15-year-old boy who was also found unconscious had, according to friends, released propane gas from his family's gas grill into a plastic bag and inhaled it. The boys had also experimented with "torch breathing," in which they exhaled the gas and ignited it. The one boy died. He suffered no burns, however, the postmortem findings included propane in the boy's blood and lung tissue.

Inhalation of volatile substances can cause death by direct toxic effects, asphyxia, aspiration of gastric contents, or trauma.

Recreational drug abuse increased the risk of stroke in young adults

In a retrospective study performed at San Francisco General Hospital, Kaku and Lowenstein determined that, "in an urban population . . . , recreational drug abuse is a prominent and growing risk factor for strokes in young adults" (*Ann Intern Med* 1990; 113:821-827). The authors' goal was to identify the records of all patients aged 15-44 years who had been admitted to the hospital for a first stroke between 1979 and 1988, and to compare the risk factors for stroke with age- and sex-matched controls. This yielded 214 matched pairs, and a mean age of 35.4 years, for both the stroke and control patients.

"Among the entire study group, cardiac conditions predisposing to embolism had the highest relative risk for stroke . . . , followed by drug abuse, diabetes mellitus, and hypertension" However, for stroke patients less than 35 years of age, the most common predisposing condition was drug abuse, and it was evident in 47% of these patients. The greatest risk for stroke occurred during the first six hours after drug abuse and diminished with time. The drug abusing patients most commonly reported the use of cocaine, followed by heroin, amphetamine, methylphenidate, and phencyclidine. Of concern to the authors was that "The proportion of patients with strokes involving drug abuse increased over the 10-year study period."

Reviewing the data on oral contraceptives and breast cancer

There have been numerous studies attempting to establish or negate an association between oral contraceptive

use and the subsequent risk of breast cancer. Despite the volumes of data published, this remains a controversial issue. Romieu et al compiled "all available epidemiologic studies of oral contraceptive use and breast cancer published in English and French" via a computerized literature search for 1966-1989 and by reviewing the references of previous articles (*Cancer* 1990; 66:2253-2263).

In their statistical analysis of these studies, the authors accounted for the age ranges of the patients and the years during which the studies were performed, in consideration of the following variables: "the latency period of the carcinogenic process . . . the formulation of the pill . . . that risk factors for breast cancer may differ according to menopausal status," and "time of exposure with regard to a woman's reproductive life . . ."

Overall, the findings revealed no increased risk of breast cancer among women who had ever used oral contraceptives, regardless of the duration of use. However, use of oral contraceptives for a long period was associated with an increased risk of premenopausal breast cancer (with an average increase in risk of 46% for ten years' use). Furthermore, this risk was seen mainly among women who used oral contraceptives prior to their first full-term pregnancy.

The explanation for this finding is not clear. It could imply a greater hormonal influence on pre- versus postmenopausal breast cancer. Or, it could "reflect a cohort effect" because oral contraceptives were not yet widely prescribed when the postmenopausal group were young women. In addition to further analysis of this finding, future studies are needed to evaluate the risks from the relatively recent low-dose contraceptives that contain ethinyl estradiol.

Esophageal obstruction caused by a fiber-based diet pill

A 70-year-old man sought emergency treatment for his sudden inability to swallow (*Gastroenterology* 1990; 99:1820-1822). He had had dysphagia to incompletely chewed solid food for six years, and testing had revealed a hiatal hernia.

On the morning of admission, he had ingested three over-the-counter anorectic tablets with a glass of water. Fifteen minutes later, after eating two spoonfuls of cereal for breakfast, he was unable to swallow food or saliva.

A barium swallow demonstrated a 2 x 3-cm mass lesion in the distal esophagus, with minimal barium passing the lesion. Sublingual nitroglycerin and nifedipine to relax the muscles and subcutaneous glucagon to lower the esophageal sphincter pressure were all ineffective in relieving the symptoms.

Following sedation, esophagogastroduodenoscopy led to the finding of a large white gelatinous mass, which was broken up with a polypectomy snare and propelled into the stomach with the end of the endoscope.

The diet pill was a "guar gum composed of the endosperm of *Cyanopsis tetragonolopus*." The authors recommend that persons with a history of esophageal stricture avoid anorectics containing fiber products that can swell.

PDR, Merck Manual available on one database

Physicians can now access the *Physicians' Desk Reference* (PDR) and *The Merck Manual* on one compact disk, read only memory (CD-ROM) database (Medical Economics Data, Oradell, NJ). A word search will simultaneously produce disease and related drug information. The drives for the CD-ROM connect via cable to an interface board installed in the expansion slots of a personal computer.

Technetium sheds light on heart damage

Technetium-based compounds are proving effective in visualizing myocardium that is not receiving an adequate blood supply. In recent months, the Food and Drug Administration (FDA) has approved the use of technetium imaging agents developed by Bristol-Myers Squibb and Du Pont Merck Pharmaceutical (*Science News* 1991; 139:4).

These agents employ technetium-99m, a radioactive compound, together with a chemical that binds to the myocardium. After injection, the imaging agent travels to the heart; pictures taken with a gamma-ray imaging camera depict the ability of the radioactive compound to bind to various regions of the heart. Absence of radioactivity represents areas of impaired blood flow and damaged heart muscle.

The imaging agent will remain bound to cardiac muscle cells for approximately four hours, thereby allowing physicians time to stabilize the patient's condition, and enabling them to evaluate the therapeutic alternatives and monitor the effectiveness of initial treatments.

Cases of acute rheumatic fever are on the rise

Within the past several years, there have been reports of a resurgence of acute rheumatic fever (ARF) in various regions of the United States. Leggiadro et al provided another example of this resurgence in their review of 30 inpatients with a discharge diagnosis of ARF from 1982 through 1988 from a children's hospital in Memphis, Tenn (*South Med J* 1990; 83:1418-1420).

There was a significant ($p < 0.001$) difference between the rate of ARF cases per 1,000 hospital discharges for the years 1982-1986 (0.15) and the rate for 1987-1988 (0.7). The mean age of the 30 patients was about nine years (range, 4 to 16 years), and the majority of patients (23/30) were black. Of the 21 patients with ARF seen from 1987 to 1988, 13 had polyarthritides and 12 had carditis.

"We believe our data demonstrate a resurgence of ARF in the mid-South area," conclude the authors, and they recommend that physicians maintain a high index of suspicion for streptococcal pharyngitis. Verification of negative rapid antigen detection tests is essential. Positive results of a standard throat culture must be followed by appropriate therapy to prevent progression to acute rheumatic fever.

Total skin examination targets a variety of skin lesions

In theory, regular total skin examinations should enable dermatologists to detect a substantial number of malignant and premalignant lesions, as well as other skin disor-

ders in patients not evidently at increased risk for such skin conditions. As part of a skin cancer awareness program that included "recommendations for sun protection, monthly self examination, yearly physician examination, and treatment of skin lesions found incidentally on the total skin examination (TSE)," Lee et al evaluated biopsy findings and patient compliance for 874 patients (*Cancer* 1991; 67:202-205). They found TSE to be a valuable tool, primarily for all new patients and once a year for all return patients. A mere 6% of 50 randomly chosen patients exposed to the skin cancer awareness program followed the stated recommendations, and 4.2% of 524 randomly selected patients returned for a yearly TSE.

The awareness program included a formal education program, usually conducted by a nurse, written information, diagrams depicting the proper method for self-examination, and the option of TSE. Of the 707/874 (80.9%) patients who underwent TSE, 151 (21.4%) had "important incidental findings"—defined as malignant or premalignant lesions, premalignant actinic keratosis, dysplastic nevi, or congenital nevi. Biopsies on 24 patients all confirmed the presence of malignant tumors.

Although the majority of the basal cell carcinomas were located on parts of the body that would be visible without removing the patient's clothing, TSE proved itself to be a valuable component of a dermatologic examination: more than one quarter of the basal carcinomas, the one malignant melanoma, the squamous cell carcinoma, and most of the 20 dysplastic nevi were found on areas normally covered by clothing.

Residents relate their thoughts on AIDS

The projection that by 1993 approximately 600,000 HIV-seropositive persons will require treatment leads to questions of the availability of physicians adequately trained and willing to diagnose, treat, and counsel these patients. A survey of 1,745 senior medical residents in internal and family medicine programs in ten states sought information on the residents' experiences and attitudes in caring for patients with AIDS and their plans for providing such care in their future medical practices (*Ann Intern Med* 1991; 114:23-32).

Seventy-three percent of respondents believed themselves to be competent in providing primary care to patients with AIDS, while 51% found their training in ambulatory care to be deficient. Treating patients with AIDS was "an excellent educational experience" for about 75% of the residents surveyed.

Sixty-seven percent expected primary care for patients with AIDS to be a component of their future practices. Experience with outpatients with AIDS during residency training was statistically associated with an increased likelihood of future plans to treat patients with AIDS; there was no such association for inpatient experiences.

The authors describe as "truly alarming" the number of needlestick injuries reported in this survey. A blood-contaminated needlestick at least once during training was reported by 72% of respondents, while 9% cited such an incident involving an HIV-seropositive patient. Twenty percent of the needlestick injuries involved patients at risk for HIV infection with unknown antibody status.

Luis Antonio Amill, MD, Sea Girt, New Jersey. Died November 29, 1990; age 92. Dr Amill was a 1921 graduate of Columbia University College of Physicians and Surgeons, New York. His memberships included the New York Academy of Medicine, the International Society of Hematology, the New York County Medical Society, and the Medical Society of the State of New York.

Morris Astrachan, MD, Brooklyn. Died December 12, 1990; age 97. Dr Astrachan was a 1919 graduate of Columbia University College of Physicians and Surgeons, New York. He was a Diplomate of the American Board of Pediatrics. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Joseph Ralph Brandy, Jr, MD, Ogdensburg. Died October 1, 1990; age 62. Dr Brandy was a 1954 graduate of Duke University School of Medicine, Durham, North Carolina. Dr Brandy was a Fellow of the American College of Obstetricians and Gynecologists and a Diplomate of the American Board of Obstetrics and Gynecology. He was a member of the Medical Society of the County of St Lawrence and the Medical Society of the State of New York.

Nicholas F. Brignola, MD, Troy. Died July 29, 1990; age 84. Dr Brignola was a 1932 graduate of Albany Medical College. He was a member of the Medical Society of the County of Rensselaer and the Medical Society of the State of New York.

Alfred Edinburg, MD, Boca Raton, Florida. Died November 27, 1990; age 65. Dr Edinburg was a 1951 graduate of Columbia University College of Physicians and Surgeons, New York. He was a Fellow of the American College of Surgeons. His memberships included the American Society of Colon and Rectal Surgeons, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Norbert Fethke, MD, Dusseldorf, Germany. Died August 10, 1990; age 86. Dr Fethke was a 1938 graduate of Université de Pierre et Marie Curie (Paris VI) U.E.R. Brossais-Hotel-Dieu, Paris. He was a Diplomate of the American

Board of Ophthalmology. His memberships included the New York Society for Clinical Ophthalmology, the New York Ophthalmology Society, the American Academy of Ophthalmology and Otolaryngology, the Pan American Association of Ophthalmology, the Pan American Medical Association, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Gregory A. Galvin, MD, Brooklyn. Died January 1, 1990. Dr Galvin was a 1937 graduate of Meharry Medical College School of Medicine, Nashville, Tennessee. He was a Fellow of the American Academy of Physicians. He was a member of the American Geriatrics Society, the Medical Society of the County of Tompkins, and the Medical Society of the State of New York.

Claudio Gerbi, MD, New York. Died December 11, 1990; age 83. Dr Gerbi was a 1931 graduate of Facolta di Medicina e Chirurgia, Università di Milano, Milano, Italy. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Ernest Bert Hofman, MD, Sarasota, Florida. Died December 8, 1990; age 93. Dr Hofman was a 1922 graduate of Medizinische Fakultät, Albert Ludwigs Universität, Freiburg im Breisgau, Baden-Württemberg, Germany. He was a Fellow of the American College of Cardiology. He was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Henry J. Kaplan, MD, Spring Valley. Died October 1, 1990; age 83. Dr Kaplan was a 1934 graduate of Boston University School of Medicine. He was a member of the Medical Society of the County of Rockland and the Medical Society of the State of New York.

Henry M. Karlan, MD, Margate, Florida. Died August 25, 1990; age 79. Dr Karlan was a 1936 graduate of Medizinische Fakultät, Universität Zürich, Zürich, Switzerland. He was a Fellow of the American Academy of Family Physicians. He was a member of the Medical Society of the County of Rockland and the Medical Society of the State of New York.

George G. Mauler, MD, Cortland. Died November 19, 1990; age 56. Dr Mauler was a 1960 graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania. He was a Fellow of the American College of Surgeons, a Qualified Fellow of the International College of Surgeons, and a Diplomate of the American Board of Orthopedic Surgery. He was a member of the American Academy of Orthopaedic Surgeons, the Cortland County Medical Society, and the Medical Society of the State of New York.

James Franklin Norton, MD, East Aurora. Died November 15, 1990; age 72. Dr Norton was a 1945 graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania. He was a Fellow of the American Academy of Family Physicians. He was a member of the Medical Society of the County of Erie and the Medical Society of the State of New York.

Lewis E. Schottenfeld, MD, Hollywood, Florida. Died December 7, 1990; age 88. Dr Schottenfeld was a 1929 graduate of McGill University, Faculty of Medicine, Montreal, Quebec, Canada. He was a Fellow of the American College of Surgeons, a Qualified Fellow of the International College of Surgeons, and a Diplomate of the American Board of Surgery. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Byron Chappleese Smith, MD, New York. Died December 6, 1990; age 82. Dr Smith was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. His memberships included the New York Academy of Medicine, the New York Ophthalmology Society, the American Academy of Ophthalmology and Otolaryngology, the American Ophthalmological Society, the Society for Experimental Biology and Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

Sidney Harvey Taylor, MD, Staten Island. Died December 9, 1990; age 83. Dr Taylor was a 1932 graduate of St Louis University School of Medicine, St Louis, Missouri. He was a Fellow of

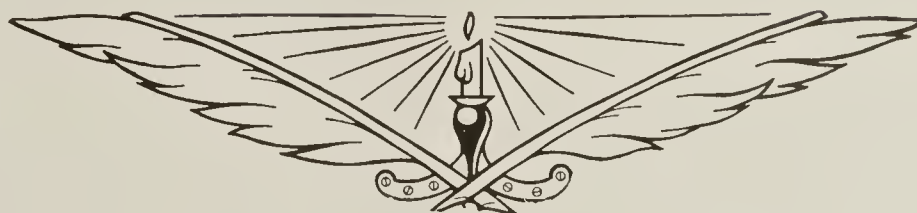
the American College of Obstetricians and Gynecologists. He was a member of the Richmond County Medical Society and the Medical Society of the State of New York.

Theodore L. Tetenbaum, MD, Yonkers. Died November 25, 1990; age 60. Dr Tetenbaum was a 1956 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Internal Medicine. He was a member of the New York Acade-

my of Medicine, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

F. Stafford Wearn, MD, Statesville, North Carolina. Died December 5, 1990; age 83. Dr Wearn was a 1932 graduate of Harvard Medical School, Boston, Massachusetts. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Edward A. Wolfson, MD, Binghamton. Died December 2, 1990; age 65. Dr Wolfson was a 1953 graduate of Cornell University Medical College, New York. He was a Fellow of the American College of Physicians and the American College of Preventive Medicine, and a Diplomate of the American Board of Internal Medicine. He was a member of the American Society of Internal Medicine, the Broome County Medical Society, and the Medical Society of the State of New York.



Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media, and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1988; 88:456-462). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal's* particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 3,000 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 1,000 and 1,500 words. Other kinds of original essays should not exceed 2,500 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with *Système Internationale* (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith² reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear in the text. When there are three or fewer authors, all should be listed; where there are four or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925-927.
2. Behrman RE, Vaughn VC: *Nelson Textbook of Pediatrics*, ed 12. Philadelphia, WB Saunders Co, 1983, pp 337-338.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Pascal James Imperato, MD, Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

MEDICAL SOCIETY OF THE STATE OF NEW YORK

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HOUSE OF DELEGATES

May 9 through May 12, 1991
Hyatt Regency Hotel
Buffalo, New York

SCHEDULE OF SESSIONS

Thursday, May 9, 1991

Opening Session 1:00 p.m.

Friday, May 10, 1991

Reference Committee Hearings ... 8:30 a.m.-5:00 p.m.

Saturday, May 11, 1991

Second Session 9:00 a.m.

Third Session 1:30 p.m.

Sunday, May 12, 1991

Closing Session 9:00 a.m.

A Guide to the 1991 Annual Meeting

Policy-making in the House of Delegates

This section of the New York State Journal of Medicine is a call to the officers, delegates, and members of the Medical Society of the State of New York to attend the 185th Annual Meeting of the Society and the meeting of its House of Delegates; 312 delegates representing 61 county medical societies, 9 district branches, specialty societies, the hospital medical staff section, 12 medical schools, the young physician, resident physician, and the medical student membership will meet at the Hyatt Regency Hotel in Buffalo on May 9-12, 1991.

The officers, members of the Council and the Board of Trustees, past presidents of the MSSNY, the Commissioner of the New York State Department of Health, the Past President of the American Medical Association from New York, Gerald D. Dorman, MD, Past Executive Vice-President of the Medical Society of the State of New York, George J. Lawrence, Jr., MD, and Past Deputy Executive Vice-President of the Medical Society of the State of New York, Robert J. O'Connor, MD, are also official representatives to the House.

Mandated by the Bylaws of the Society, this section lists the names of elected representatives, delegates who are serving on reference committees, and selections of the Nominating Committee for the election of Officers, Councilors, Trustees and AMA Delegates. Also included are the amendments to the Bylaws which will be considered by the House of Delegates.

Since the House of Delegates is the legislative body of the Society, charged with the general management of the State Society and its affairs, members of the Society are urged to use this information to consult with and advise their representatives. Resolutions introduced by the representatives bring members' concerns to the attention of the entire Society. Representatives not only have the responsibility to present the views of their constituents, but also to inform them of the actions taken by this governing body. The House of Delegates also formulates policy for the Society. No officer, councilor, board, commission, committee, or employee may initiate any policy unless such policy has been expressly approved by the House of Delegates, or by the Council of the Society.

If one were to choose the most important work of the House of Delegates, it would have to be that of the reference committees. Any member of the Medical Society of the State of New York has the right to appear before any reference committee and participate in its deliberations. It is also in the reference committees that people outside of the State Society are asked to give their views. Nonmember physicians, guests or interested observers who wish to express their opinions may, with permission, come before the reference committee and speak to the business of the committee. I strongly urge members to use this forum to express their views.

Seymour R. Stall, M.D., Speaker
House of Delegates

John H. Carter, M.D., Vice-Speaker
House of Delegates

MEDICAL SOCIETY OF THE STATE OF NEW YORK



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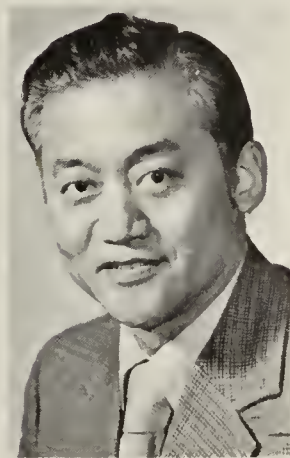
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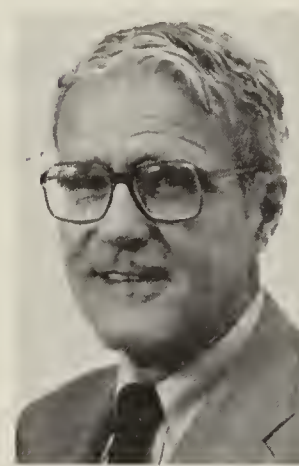
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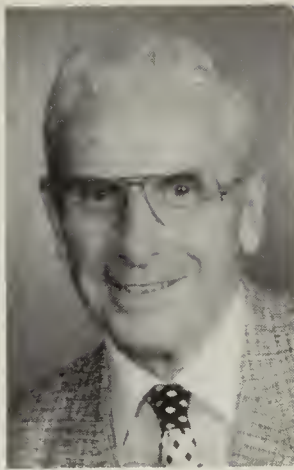
Dutchess
Speaker



John H. Carter, MD

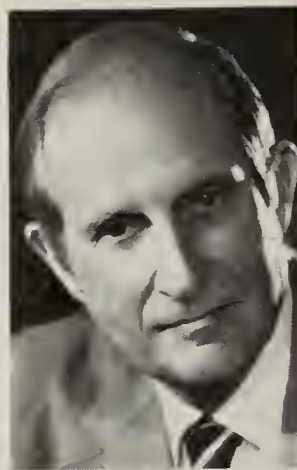
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Allison B. Landolt, MD

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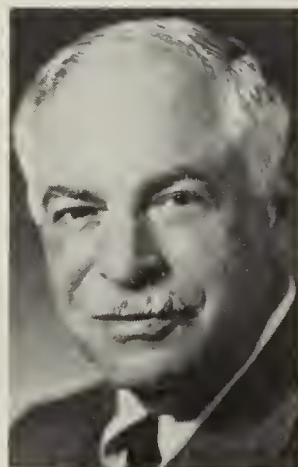
James M. Flanagan, MD

Wayne



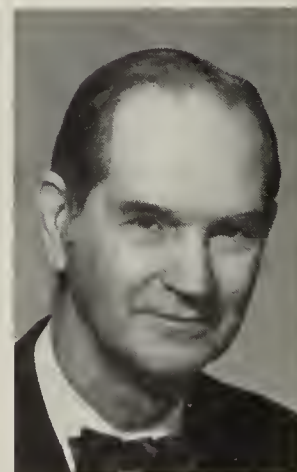
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Nassau



M. Theodore Tanenhaus, MD

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Charles D. Sherman, Jr., MD

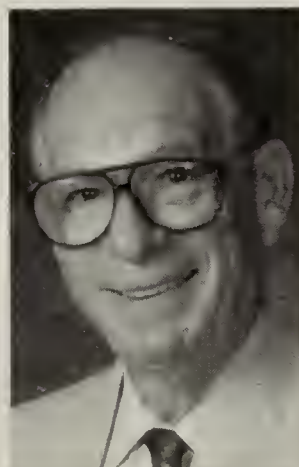
Monroe

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Warren



Sidney Mishkin, MD

Nassau



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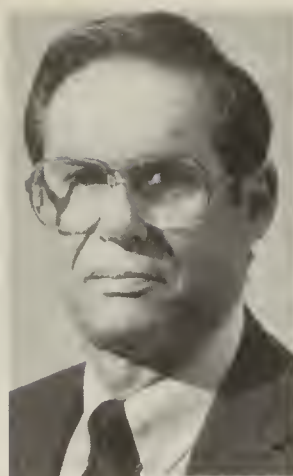
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Thomas D. Pemrick, MD

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New York



Malcolm D. Reid, MD

New York



Matthew J. Kleinerman

New York

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Term Expires 1992

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Thomas D. Pemrick, Rensselaer
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Term Expires 1993

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New York State Society of Anesthesiology—Edward C. Sinnott, Nassau
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New York Chapter American College of Emergency Physicians—Jeffrey L. Margulies, Suffolk

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 New York State Society of Orthopaedic Surgeons, Inc.—Leo Arthur Green, Queens
 New York State Society of Otolaryngology—Head and Neck Surgery—
 New York State Society of Pathologists—
 American Academy of Pediatrics—District II—
 New York Society of Physical Medicine and Rehabilitation, Inc.—
 New York Regional Society of Plastic and Reconstructive Surgery—Arthur Wise, Nassau
 New York State Psychiatric Association—
 The New York State Radiological Society, Inc. (A Chapter of the American College of Radiology)—Jerome Zwanger, Nassau
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 New York State Urological Society, Inc.—Marcus L. Shoobe, Albany

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Livingston (1)

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Montgomery (2)

Nassau (11)

Paul B. Bedrossian, Rockville Centre
Robert Bruce Bergmann, Massapequa
Lee S. Binder, Valley-Stream
Paul A. Hamlin, Great Neck
Arnold D. Lurie, Baldwin
Sharon C. Mead, Massapequa
Felix A. Monaco, Rockville Centre
John A. Ostuni, Freeport
E. John Pesiri, Massapequa
Leonard S. Weiss, Levittown

New York (24)

Arnold L. Bachman, New York
Melvin H. Becker, New York
Robert S. Bernstein, New York
Michael B. Brodin, New York
Valentine J. Burroughs, New York

Anthony A. Clemendor, New York
Irwin J. Cohen, New York
Joseph E. Davis, New York
Jonas M. Goldstone, New York
Michael H. Grieco, New York
George Hyams, New York
Virginia Kanick, New York
Vance Lauderdale, Jr., New York
Samuel H. Madell, New York
Aaron G. Meislin, New York
Donna B. O'Hare, New York
Marilyn Pearl, New York
William B. Rawls, Pleasant Valley
William B. Rosenblatt, New York
Clifford L. Spingarn, New York

Niagara (3)

Mary Ann Z. Bishara, Lewiston
James J. Kropelin, Niagara Falls
Robert Reszel, Tonawanda

Oneida (4)

Sidney J. Blatt, New Hartford
Charles M. Brown, Rome
Neville W. Harper, Rome
Kenneth K. Kim, Utica

Onondaga (7)

Duane M. Cady, Liverpool
Armand J. Cincotta, Liverpool
Daniel L. Dombroski, Syracuse
John A. Hoepner, Syracuse
Richard A. Konys, Syracuse
Frank J. Piper, Syracuse
George P. Tilley, Syracuse

Ontario (2)

Verne M. Marshall, Geneva
Kenneth T. Steadman, Geneva

Orange (4)

Fritz Beauboeuf, Middletown
Stanley F. Brunn, Port Jervis
Michael A. Parmer, Port Jervis
Seymour J. Weiner, Port Jervis

Orleans (1)

David B. L. Meza III, Albion

Oswego (1)

Corliss Varnum, Oswego

Otsego (3)

Rodman D. Carter, Cooperstown
John O. Lusins, Oneonta
Jonathan Sastic, Oneonta

Putnam (1)

Queens (16)

Marvin L. Blumberg, Jamaica

Daniel Chansky, Forest Hills
 John W. V. Cordice, Jr., St. Albans
 Daniel G. Deckler, Richmond Hill
 Alexander M. De le Garza, Flushing
 Fred S. Fensterer, Glendale
 Fred N. Flatau, Flushing
 Lorraine M. Giordano, Jamaica Estates
 Victor Guarneri, Bayside
 Nicetas H. Kuo, Great Neck
 Maxwell J. Marder, Forest Hills
 Jean P. Papps, Jamaica
 Frank Ratner, Flushing
 Hilda Ratner, Beechurst
 Sheldon D. Sax, Whitestone
 Ezra A. Wolff, Manhasset

Rensselaer (2)

Arsenio G. Agopovich, Watervliet
 William A. Whyland, Troy

Richmond (4)

Robert Bonvino, Staten Island
 Zoltan Brody, Staten Island
 Tano S. Carbonaro, Staten Island
 Gerald J. Lustig, Staten Island

Rockland (4)

Herbert Z. Geller, New City
 Paul S. Mercurio, New City
 Stanley H. Oransky, Bardonia
 Robert S. Siebken, New City

St. Lawrence (1)

Ravinder Agarwal, Ogdensburg

Saratoga (1)

Allen T. Jones, Saratoga

Schenectady (3)

George J. Giokas, Schenectady
 Richard H. Lange, Schenectady
 Robert J. Pletman, Schenectady

Schoharie (1)

Frederick J. Michel, Cobleskill

Schuyler (1)

Seneca (1)

Steuben (2)

M. Al-Hussaini, Hornell
 Jack D. O'Neil, Corning

Suffolk (11)

Christopher J. Beatty, Port Jefferson
 Bruce H. Berlin, Huntington
 Stephen I. Braitman, Islip Terrace
 Clive D. Caplan, Islip Terrace
 Frank R. Collier, Port Jefferson
 John G. Egner, West Islip
 Philip A. Mantia, Smithtown
 Martin Matalon, Bay Shore
 Gerard F. Ryan, Patchogue

Stanley A. Steckler, Smithtown
 William H. Weir, Jr., Riverhead

Sullivan (1)

Paul D. Salzberg, Callicoon

Tioga (1)

Tompkins (2)

Robert A. Hesson, Ithaca
 Elliot Rubinstein, Ithaca

Ulster (2)

Stephen L. Hermele, Kingston
 Fred Horwitz, Ellenville

Warren (3)

Washington (1)

Barney Rubenstein, Cambridge

Wayne (3)

Westchester (9)

Ann C. Cea, Rye Brook
 Mark L. Fox, Bronxville
 Sanford A. Kaplan, Bronxville
 Thomas A. Lansen, Valhalla
 Robert C. Mickatavage, Rye
 Toni G. Novick, New Rochelle
 Stephen O. Schwartz, White Plains
 Pellegrino J. Tozzo, New Rochelle
 William J. Walsh, Jr., White Plains

Wyoming (1)

Yates (1)

Medical School Delegates (12)

Albany Medical—Henry S. Pohl, Albany
 Albert Einstein College of Medicine of Yeshiva University of New York—
 Columbia University College of Physicians and Surgeons—Linda D. Lewis, New York
 Cornell University Medical College—
 Mount Sinai School of Medicine of the City University of New York—
 New York Medical College—Susan Anderson Kline, Valhalla
 New York University of Medicine—
 State University of New York Health Science Center at Brooklyn—
 State University of New York at Buffalo School of Medicine—Dennis Nadler, Buffalo
 State University of New York at Stony Brook School of Medicine—
 State University of New York Health Science Center at Syracuse—
 John Bernard Henry, Syracuse
 University of Rochester School of Medicine and Dentistry—Philip P. Bonanni, Rochester

Medical Student Delegates (3)

Roger Frankel, New York
 Allan Klapper, New York
 Faheem Sandhu, Rochester

Resident Membership Delegate (1)

Mitchell Miller, Schenectady

Young Physician Delegate (1)

John F. Piper, Onondaga

Hospital Medical Staff Delegate (1)

Vicki Lynn Seltzer, Nassau

REFERENCE COMMITTEES

Reports of Officers and Administrative Matters

John B. Henry, MD, SUNY Health Science Center at
Syracuse, *Chairman*
Robert A. Hesson, MD, Tompkins
Sharon Mead, MD, Nassau
Abdul Rehman, MD, Kings
Jerome Zwanger, MD, The New York State Radiological
Society
Florian Cortese, Dutchess (Observer)

Bylaws

Samuel Madell, MD, New York, *Chairman*
Sana Bloch, MD, The Bronx
Stanley F. Brunn, MD, Orange
Ann Cea, MD, Westchester
Elise Korman, MD, New York State Academy of
Family Physicians
Armand J. Cincotta, MD, Onondaga (Observer)

Governmental Affairs and Legal Matters

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Leo Arthur Green, MD, New York State Society of
Orthopaedic Surgeons
Thomas A. Lansen, MD, Westchester
Donna B. O'Hare, MD, New York
John A. Ostuni, MD, Nassau
Kenneth T. Steadman, MD, Ontario (Observer)

Socio-Medical Economics

James J. Kropelin, MD, Niagara, *Chairman*
Bruce Berlin, MD, Suffolk
David T. Hannan, MD, Wayne
Mitchell Miller, MD, Resident Physician Section
James H. Puleo, MD, Albany
Herbert Z. Geller, MD, Rockland (Observer)

Scientific and Educational Activities

Nancy H. Nielsen, MD, PhD, Erie, *Chairwoman*
Robert Bonvino, MD, Richmond
Alan Klapper, Medical Student Section
Michael A. Parmer, MD, Orange
William Rosenblatt, MD, New York
John Cordice, MD, Queens (Observer)

Hospital and Medical Facilities

Eleanor C. Kane, MD, Dutchess, *Chairwoman*
Mark L. Fox, MD, Westchester
Robert Kohn, MD, New York State Society of
Internal Medicine
David B. L. Meza III, MD, Orleans
Anton A. Vreede, MD, Sixth District Branch
Lorraine Giordano, MD, Queens (Observer)

CONVENTION COMMITTEES

Credentials

Clive D. Caplan, MD, Suffolk, *Chairman*
W. Bruce Carter, MD, Jefferson
Alexander M. De la Garza, MD, Queens
Dattatraya G. Lanjewar, MD, The Bronx
Charles Rubin, MD, Broome
John Piper, Young Physician Section (Observer)

Sergeant at Arms

Feori F. Pipito, MD, Montgomery, *Chairman*
Albert B. Accettola, MD, First District Branch
Richard Freeman, MD, Cayuga
Robert J. Pletman, MD, Schenectady
Jagdish Wadhwa, MD, Dutchess
William B. Rawls, MD, New York (Observer)

Rules and Order of Business

Venkatachala Pathy, MD, The Bronx, *Chairman*
Albert M. Ellman, MD, Third District Branch
Ladislav P. Hinterbuchner, MD, Kings
Mario B. LoMonaco, MD, Monroe
William Wittlin, MD, Cortland
Arnold D. Lurie, MD, Nassau (Observer)

Tellers

David O. Van Eenenaam, MD, Jefferson, *Chairman*
Michael Brodin, MD, New York
John Hoepner, MD, Onondaga
Frederick J. Michel, MD, Schoharie
Judithann Pryce, MD, Kings
Michal Amir, Medical Student Section (Observer)

NOMINATING COMMITTEE

To the House of Delegates, Ladies and Gentlemen:

In accordance with Article XI, Section 2 of the Bylaws of the Medical Society of the State of New York, the Nominating Committee met at the Society's headquarters, 420 Lakeville Road, Lake Success, New York, on Wednesday, November 7, 1990 at 11:00 a.m.

Members of the Committee present were:

Member-at-Large—**John A. Finkbelner, M.D.**, New York, *Chairman*

First District Branch—**Ralph E. Schlossman, M.D.**, Queens

Second District Branch—**Stanley A. Steckler, M.D.**, Suffolk

Third District Branch—**Stephen L. Hermele, M.D.**, Ulster

Fourth District Branch—**William Busino, Jr., M.D.**, Schenectady

Fifth District Branch—**Duane M. Cady, M.D.**, Onondaga

Sixth District Branch—**Antonio F. LaSorte, M.D.**, Broome

Seventh District Branch—**Joyce M. McChesney, M.D.**, Monroe

Eighth District Branch—**James J. Kropelln, M.D.**, Erie

Ninth District Branch—**Pellegrino J. Tozzo, M.D.**, Westchester

Member-at-Large—**John A. Ramsdell, M.D.**, Westchester

After careful consideration of the recommendations submitted by the district branches, the county medical societies, and the resident and student sections in response to a memorandum, dated June 29, 1990, your Committee respectfully nominated the following candidates for election on May 5, 1991:

President—**Charles N. Aswad, M.D.**, Broome

President-Elect—**Morton M. Kurtz, M.D.**, Queens

Vice-President—**Stanley A. Steckler, M.D.**, Suffolk

Secretary—**George Lim, M.D.**, Oneida

Assistant Secretary—**Joyce M. McChesney, M.D.**, Monroe

Treasurer—**James H. Cosgriff, Jr., M.D.**, Erie

Assistant Treasurer—**Antonio F. LaSorte, M.D.**, Broome

Speaker—**Seymour R. Stall, M.D.**, Dutchess

Vice-Speaker—**John H. Carter, M.D.**, Albany

Councilors (four for three years):—**Robert B. Bergmann, M.D.**, Nassau

—**Richard A. Hughes, Sr., M.D.**, Warren

—**Jeffrey A. Ribner, M.D.**, Broome

—**Anthony P. Santomauro, M.D.**, Erie

Resident Councilor (one for one year):—**Paul A. Pipia, M.D.**, Richmond

Student Councilor (one for one year):—* **Matthew H. Kleinerman**, New York

Trustee (one for five years):—**Duane M. Cady, M.D.**, Onondaga

Nomination for one-year term for AMA Resident Physician Alternate Delegate

(Term: January 1, 1992–December 31, 1992)—**Stuart B. Kahn, M.D.**, New York

Nomination for one-year term for AMA Student Alternate Delegate

(Term: January 1, 1992–December 31, 1992)—**Haroon Choudhri**,* New York

Nominations for AMA Delegates—1/1/92 to 12/31/93—and nominations for AMA Student Delegates*—1/1/92 to 12/31/92:

John H. Carter, M.D., Albany

Ann C. Cea, M.D., Westchester

Duncan W. Clark, M.D., Kings

James H. Cosgriff, Jr., M.D., Erie

John A. Finkbelner, M.D., New York

James M. Flanagan, M.D., Wayne

* **Dawn Gangl**, The Bronx

Samuel M. Gelfand, M.D., Nassau

Robert M. George, M.D., Oneida

Edmond J. Glcewicz, M.D., Erie

Morton M. Kurtz, M.D., Queens

Allison B. Landolt, M.D., Westchester

Antonio F. LaSorte, M.D., Broome

George Lim, M.D., Oneida

David B. L. Meza III, M.D., Orleans

Nancy H. Nielsen, M.D., Ph.D., Erie

Stuart I. Orsher, M.D., J.D., New York

Bernard J. Pisani, M.D., New York

Patricia A. Randall, M.D., Onondaga

Nathan P. Reed, M.D., Albany

Charles D. Sherman, Jr., M.D., Monroe

Seymour R. Stall, M.D., Dutchess

M. Theodore Tanenhaus, M.D., Kings

Victor J. Tofany, M.D., Monroe

The twelve nominees receiving the largest number of votes will be delegates; the second twelve will be alternates.

Respectfully submitted:

John A. Finkbeiner, M.D., *Chairman*

* Medical Student

HOUSE COMMITTEE ON BYLAWS

To the House of Delegates, Ladies and Gentlemen:

The members of the House Committee on Bylaws are as follows:

George Lim, M.D., Chairman Oneida
Stanley F. Brunn, M.D. Orange
Rodman D. Carter, M.D. Otsego
Robert M. Kohn, M.D. Erie
Sidney Mishkin, M.D. Nassau
Donna B. O'Hare, M.D. New York
Marilyn Pearl, M.D. New York
Hilda Ratner, M.D. Queens
Stanley A. Steckler, M.D. Suffolk
Robert A. Mayers, M.D., ... President,
..... ex officio, Westchester
Seymour R. Stall, M.D., ... Speaker,
..... ex officio, Dutchess
Donald F. Foy ... Executive Vice-President, ex officio
William R. Egan Deputy Exec.
..... Vice President, ex officio
Donald R. Moy, Esq. General Counsel, ex officio

A meeting of the Reference Committee on Bylaws was held at the Hilton Hotel in New York City on March 30, 1990. The Reference Committee prepared a transcript of testimony and a summary of its recommendations to the House Committee on Bylaws. The input received from the meeting of the Reference Committee on Bylaws proved to be of great assistance to the House Committee on Bylaws when it met on November 8, 1990.

Two resolutions asking for amendments to the Bylaws were referred to the Committee for consideration.

Resolution 90-73, Designated AMA Delegate and Alternate Delegate from the Medical Student Section of MSSNY

Introduced by the MSSNY Medical Student Section

Whereas, Medical students contribute substantially to the membership of both the Medical Society of the State of New York and the American Medical Association; and

Whereas, The state medical societies of Texas, Massachusetts, California and Ohio have slotted seats in their AMA Delegations for medical students; and

Whereas, In each year since 1982 at least one medical student has served as an alternate delegate in New York's delegation to the AMA/HOD; and

Whereas, Serving as an alternate delegate to the AMA/HOD has proven an invaluable experience for medical students; therefore be it

Resolved, That Article VIII, Section 1 of the Bylaws of the Medical Society of the State of New York be amended by the addition of a new paragraph 4 to read as follows: "Each year one delegate position and one alternate delegate position shall be reserved for medical students, each for a term of one year."

and be it further

Resolved, That Article VIII, Section 1, paragraph 5 be amended to read as follows (addition italicized):

"A duly elected delegate to the American Medical Association who does not serve as such because of reduction in number of delegates to which the Medical Society of the State of New York is entitled shall fill any vacancy which may occur in the delegation before alternate delegates are designated for that purpose. *However, one delegate position and one alternate delegate position shall continue to be designated for medical students.*"

After full deliberation, the House Committee on Bylaws recommends the following substitute resolution: **Resolved**, That Article VIII, Section 1 of the Bylaws of the Medical Society of the State of New York be amended by the addition of a new paragraph 4 to read as follows: "Each year one alternate delegate position shall be reserved for a medical student who is a member of MSSNY and such student shall serve for a term of one year."

and be it further

Resolved, That Article VIII, Section 1, paragraph 5 be amended to read as follows (additions italicized):

"A duly elected delegate to the American Medical Association who does not serve as such because of reduction in number of delegates to which the Medical Society of the State of New York is entitled shall fill any vacancy which may occur in the delegation before alternate delegates are designated for that purpose. *However, one alternate delegate position shall continue to be designated for a medical student who is a member of MSSNY.*"

The House Committee on Bylaws heard testimony that reserving one delegate and one alternate delegate position for medical students will help develop future medical leadership and will stimulate greater interest among medical students to join organized medicine. The Committee also heard testimony that medical students face difficult obstacles in being elected as delegates because they are relatively unknown. The Committee agrees that reserving an alternate delegate position for a medical student will help accomplish the objective of developing future medical leadership. It is believed, however, that reserving a delegate position is unnecessary.

Accordingly, the House Committee on Bylaws unanimously recommends **ADOPTION** of the substitute resolution for Resolution 90-73.

Resolution 90-77, Councillor Representing the Hospital Medical Staff Section

Introduced by the Hospital Medical Staff Section

Whereas, Many of the regulatory issues confronting the medical profession today relate to medical practice in the hospital environment; and

Whereas, It is important to have a strong communications link between the MSSNY Council and the Society's hospital medical staff section; and

Whereas, This can best be accomplished through formal hospital medical staff section representation on the Council, and state medical societies have been encouraged by the AMA to provide for such representation; and

Whereas, The medical student and resident physician sections of the MSSNY are represented on the Council; therefore be it

Resolved, That the Bylaws of the Medical Society of the State of New York be amended to provide that the chairperson of the hospital medical staff section be a non-voting member of the MSSNY Council; and be it further

Resolved, That Article XII-A, paragraph 1 of the Bylaws of the Medical Society of the State of New York be amended to read as follows (additions italicized):

"The hospital medical staff section is authorized to be represented in the House of Delegates by one delegate, *and on the MSSNY Council by one councilor, who shall be the individual elected by the section as its chairperson.* The hospital medical staff section shall represent physicians on the medical staffs of acute care hospitals located in New York State; of psychiatric inpatient facilities maintained by the State of New York or its political subdivisions; and of hospitals with inpatient programs certified by the New York State Office of Mental Health."

and be it further

Resolved, That Article XI, Section 2, paragraph 2 under the heading "Nominating Committee" be amended to read as follows (additions italicized, deletions in brackets):

"In the event that a member of the Nominating Committee who has been selected as the representative of a particular district branch (or his alternate) shall be unable to attend the meeting of this committee, the president shall appoint an at large member, from the district branch whose representative is absent, to represent the interests of that district on the Nominating Committee. It shall be the duty of this committee to propose and nominate members of the Medical Society of the State of New York for all vacancies to be filled at the ensuing annual meeting of the House of Delegates, *with the exception of the councilor representing the hospital medical staff section.* [These] *Nominating Committee* recommendations shall be made to the House of Delegates in the same manner as prescribed in Article X, Section 1, paragraph 2."

and be it further

Resolved, That Article IV, Section 1, paragraphs 1-5 be amended to read as follows (additions italicized, deletions in brackets):

"The Council shall be composed of the president, president-elect, vice-president, immediate past-president, secretary, assistant secretary, treasurer, assistant treasurer, speaker, vice-speaker, chairman of the Board of Trustees and [14] 15 councilors elected by the House of Delegates.

"The trustees, the executive vice-president, the deputy executive vice-president, and the general counsel of the Medical Society of the State of New York shall attend all meetings of the Council with voice but without vote. The councilors from resident physician section shall attend all meetings of the Council with voice and with vote. The councilors from the medical student section *and the hospital medical staff section* shall attend all meetings of the Council with voice but without vote.

"Four councilors shall be elected annually by the House

of Delegates, each for a term of three years. Two councilors, one councilor representing the medical student section and one councilor representing the resident physician section to the Medical Society of the State of New York shall be elected every year by the House of Delegates, each for a term of one year. *One councilor representing the hospital medical staff section shall be elected every other year by the House of Delegates for a term of two years.* Article IV, Section 1, paragraph 4 is not applicable to the term of office of a resident or student councilor, *or a councilor representing the hospital medical staff section.* In the event of a vacancy, a councilor shall be elected by the Council to serve until the next meeting of the House of Delegates at which time the House of Delegates shall elect a councilor to fill the unexpired term.

"No person shall serve, consecutively, more than two terms as councilor. An unexpired term shall not be construed as a term of office.

"The councilors shall assume office on election and shall hold office until their successors are duly elected and qualified.

"Councilors, other than the councilors representing the medical student [section] and [the councilor representing] the resident physician sections, *and hospital medical staff section* shall be assigned to specific county societies as liaison for the Council in accordance with the provisions of Article V, Section 2. Councilors shall be required to disseminate information of Council activity as well as returning information to the Council, and shall report regularly to the Council on their activity. The councilor representing the medical student section must be a student member of the Medical Society of the State of New York; the councilor representing the resident physician section must be a resident member of the Medical Society of the State of New York."

Past House Action: Resolution 89-5

After thorough deliberation, the House Committee on Bylaws does not believe that the Bylaws should be amended to provide for a councilor to represent the hospital medical staff section. It is believed that the current composition of the Council is more than adequate to address the issues pertinent to hospital medical staffs.

The Committee notes that this past year, the President of the Medical Society extended an invitation to the chairperson of the hospital medical staff section to attend Council meetings as a guest. The Committee encourages future presidents of the Medical Society to continue this practice. It is not believed, however, that it is necessary to designate the chairperson of the hospital medical staff section as a councilor.

Accordingly, the House Committee on Bylaws unanimously recommends that Resolution 90-77 **NOT BE ADOPTED.**

Your Chairman would like to thank, in addition to the members of the Committee and the physicians who testified before it, those members of staff who helped this Committee: Donald R. Moy, Esq., Jay B. Silverman, Esq. and Kathy Wellborn.

Respectfully submitted,

George Lim, M.D., *Chairman*



One Of A Kind



Zantac[®]

ranitidine HCl/Glaxo 150 mg and
300 mg tablets

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/ROCHE



One Of A Kind

Zantac[®]
ranitidine HCl/Glaxo 150 mg and
 300 mg tablets

Zantac[®] 150 Tablets
 (ranitidine hydrochloride)

Zantac[®] 300 Tablets
 (ranitidine hydrochloride)

Zantac[®] Syrup
 (ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac[®] product labeling.

INDICATIONS AND USAGE: Zantac[®] is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac[®] is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac[®] therapy does not preclude the presence of gastric malignancy.

2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix[®] may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac[®]. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H₂-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocellular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

BRIEF SUMMARY

Zantac[®] 150 and 300 (ranitidine hydrochloride) Tablets
Zantac[®] (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac[®] product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac[®] 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac[®] 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac[®] 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac[®] Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

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MISCELLANEOUS

MAY 13-17, 1991. Consultant's Course in Cardiology. New York, New York. Sponsored by the American College of Cardiology, The New York State Chapter, American College of Cardiology, The New York Cardiological Society, and the Page and William Black Post Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY). 36 credit hours in Category 1. Inquiries: Registration Secretary, Extramural Programs Department, American College of Cardiology. Phone: 1-800-253-4636. FAX 301-897-9745.

(continued from p 2A)

Heart Association, 365 Willis Ave, Mineola, NY 11501. Tel: (516) 741-5522.

ROCHESTER

Apr 11-12. Non-Invasive Cardiology for Clinicians. Riverside Convention Center. Contact: University of Rochester, Office of Continuing Professional Education, 601 Elmwood Ave, Box 677, Rochester, NY 14642.

UTICA

Apr 23. Fulton County Pulmonary Teaching Day. Holiday Inn. Contact: American Lung Association of Mid-New York, 311 Turner St, Suite 145, Utica, NY. Tel: (315) 735-9225.

AROUND THE NATION

CALIFORNIA

Apr 21-26. 11th Annual San Diego Residents' Radiology Review Course. 39 Cat I Credits. **Apr 27. Introduction to Interventional Radiology.** 8 1/4 Cat I Credits. Hyatt Regency, La Jolla. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077. Tel: (404) 641-9773.

DISTRICT OF COLUMBIA

Apr 29-30. Ethical Issues in Research. Georgetown University. Contact: Fidia Research Foundation, 1640 Wisconsin Ave, NW, Suite 2, Washington, DC 20007. Tel: (202) 337-7185.

FLORIDA

Apr 19-21. Pediatric Lung Disease Conference. St Petersburg. Contact: Paula Kehrli, Nemours Children's Clinic, PO Box 5485, Jacksonville, FL 32247. Tel: (904) 390-3638.

HAWAII

Apr 7-12. Diagnostic Imaging: 1991. 22 1/2 Cat I Credits. Ritz-Carlton Mauna Lani, Kona, Hawaii. Contact: Radiology Postgraduate Education, Room C-324, University of California School

(continued on p 16A)

YOCON[®]

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

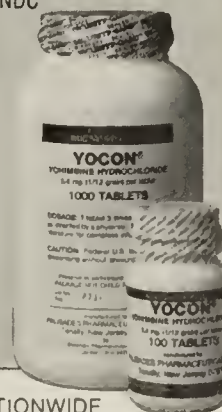
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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of Medicine, San Francisco, CA 94143.
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MARYLAND

Apr 17-21. Fifth Annual Review and Update Course in Critical Care Medicine. Crowne Plaza Hotel, Rockville. Contact: Svetlana Lisanti, Conference Administrator, Center for Bio-Medical Communication, Inc, 80 W Madison Ave, Dumont, NJ 07628. Tel: (201) 385-8080.

MASSACHUSETTS

Apr 13. Communication Approaches for Tracheostomized and Ventilator Dependent Patients. Boston. Contact: Voicing, 3857 Birch, Ste 194, Newport Beach, CA 92660. Tel: (714) 856-2419.

MISSOURI

Apr 10-13. Treatment of Surgical Spine Disease. Ritz-Carlton Hotel, St Louis, **Apr 25-26. 18th Annual Obstetrics & Gynecology Symposium.** Washington University Medical Center, St Louis. **Apr 30-May 2. Molecular Basis of Bone Cell Physiology: Transcellular Signaling.** Sheraton West Port Inn, St Louis. Contact: Cathy Caruso, Office of Continuing Medical Education, Washington University School of Medicine, 660 S. Euclid, Box 8063, St Louis, MO 63110. Tel: (800) 325-9862.

NEW JERSEY

Apr 26-27. Controversial Issues in Preventive Medicine. 18 Cat I Credits. Trump Regency, Atlantic City. Contact: Dana R. Davies, Dept of CME, Cooper Hospital/University Medical Center, 1 Cooper Plaza, SC 116, Camden, NJ 08103. Tel: (609) 342-3074.

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Apr 21-25. Diagnostic Radiology Seminar 1991. 22½ Cat I Credits. Beachcomber Parkroyal, Moorea, Tahiti. Contact: Radiology Postgraduate Education, Room C-324, University of California School of Medicine, San Francisco, CA 94143. Tel: (415) 476-5731. □

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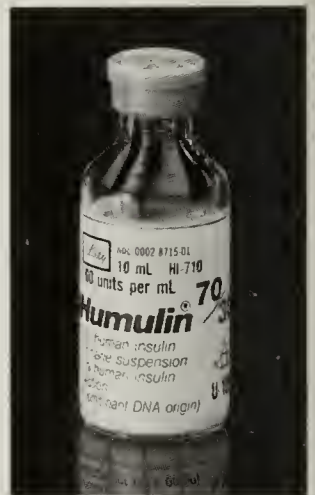
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The New York State Journal of Medicine cannot guarantee publication of meeting and lecture notices. Information must be submitted at least three months prior to the event.

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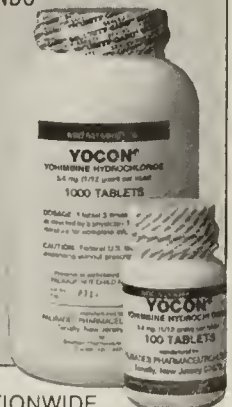
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COMMENTARIES

Cancer and the family history trail

A thoroughly compiled family history of cancer harbors the potential of being the most cost beneficial component of the patient's workup. Having said this, it is indeed surprising that the cancer family history remains the most severely neglected portion of the patient's medical evaluation. This concern instigated the study by David and Steiner-Grossman¹ which appears in this issue of the *Journal*.

This serious problem was previously documented² when the family histories of cancer of 200 consecutive cancer patients who were undergoing treatment in an oncology clinic were evaluated. Among these cases, there were numerous examples of familial cancer clusters as well as hereditary cancer syndromes. However, the review of these patients' pre-existing clinic charts demonstrated that in most circumstances the family history of cancer had either been omitted altogether or reported as negative, despite substantial evidence to the contrary. Even in those circumstances where the family history was strongly positive, the information had not been pursued or acted upon.²

This observation was no surprise, since early investigations of cancer-prone families from the patients' medical charts almost invariably showed "family history negative for cancer . . ." Yet these were kindreds showing the Cancer Family Syndrome (now known as Lynch syndrome II) wherein there was an autosomal dominantly inherited pattern of early onset colorectal carcinoma, with proximal predominance, an excess of synchronous and metachronous colonic cancer, and an integral association with carcinoma of the endometrium, ovary, and cancer of other anatomic sites.³ In short, these families were often being decimated by cancer; yet their medical records still contained reports that were "negative" for family history of cancer.

Given the public health significance of hereditary cancer where, conservatively, it is estimated that between 5% and 10% of *all* cancer occurrences in the United States will have a hereditary etiology,⁴⁻⁶ it is indeed timely that David and Steiner-Grossman have seen fit to document the general inadequacy of the family history of cancer in the clinical setting.¹ They accomplished this task through a survey of 76 acute care, nonpsychiatric hospitals in New

York City. Their survey was designed to determine if data on family history of cancer were being recorded in the medical charts in these hospitals. Soberingly, only four of the 64 reporting hospitals indicated that this information was reported in their medical records. It was even more surprising to learn that information on the family history of cancer was not a requirement of any of the hospital accrediting agencies. Even the American College of Surgeons does not have this as a requirement. Clearly, this serious omission must be rectified because we physicians are missing countless opportunities to enhance our cancer control strategies through knowledge available in the family history.

I would now like to discuss briefly the molecular genetic implications of recent cancer research. Why talk about molecular genetics in a commentary on David and Steiner-Grossman's cancer family history paper? The reason is that we are now in the midst of a most challenging, exciting, and rewarding period in the basic sciences, as evidenced by almost daily advances in molecular genetics which have direct implications for cancer etiology and control. For example, we now have an opportunity to identify the chromosomal location of any cancer-prone genes. Ultimately we will be able to clone these genes. This has already been accomplished in the case of retinoblastoma.⁷ Nevertheless, for precise clinical application of this knowledge, the family history of cancer becomes a crucial matter, with an important bearing on the following issues: 1) Who should be tested? 2) What test should be employed? 3) What specific hereditary chromosomal locus should be pursued in these tests? 4) Which additional families prone to cancer might benefit from these biomolecular advances? Finally, molecular gene probes will undoubtedly be employed to identify individuals who are genetically susceptible to specific environmental carcinogens, including those in the workplace. For example, Harris et al^{8,9} have shown that at the biomolecular level, binding levels of benzo(a)pyrene to DNA vary 50- to 100-fold in cultured human tissues and cells. This enormous variation in carcinogen metabolism in humans may be attributed to the fact that the majority of chemical carcinogens require enzymatic activation, and herein host

factors play a major etiologic role in determining variation in such enzyme capability. It has been postulated that the ratio of metabolic activation to deactivation of carcinogens may determine the individual's cancer risk.

Hereditary cancer diagnosis is obviously mandatory for this entire process. The *family history* will assume major importance in accomplishing this goal.

How much detail is required in compiling the family history? Ideally, the specific histologic type of cancer, the age at onset, and, when applicable, those phenotypic stigmata which may be associated with a particular hereditary cancer syndrome must be recorded for all first degree relatives and selected second degree relatives, including both sets of grandparents, aunts, and uncles. It is important to pursue both sides of the family because *a priori* one will not know whether the deleterious trait is being inherited through the maternal or paternal lineage. Even in such sex-limited disorders as hereditary forms of carcinoma of the breast, ovary, and endometrium, one must appreciate the fact that since these disorders are autosomal dominantly inherited, males may be harborers of the deleterious gene and thereby transmit it to their daughters. In addition, these selected second degree relatives are important in that they are generally older and therefore more likely to have passed through the cancer risk age. Thus, they will be more informative for pedigree analysis.

Virtually all hereditary cancer disorders show certain cardinal features, foremost of which are significantly early onset; an excess of multiple primary cancer, including bilaterality of paired organs; specific patterns of multiple primary cancer wherein the tumor combinations are dependent upon the hereditary disorder of concern; and Mendelian inheritance patterns of cancer transmission.⁴ This knowledge of hereditary cancer's natural history can serve the physician admirably well in developing surveillance and management programs for high risk patients. However, these diagnostic and cancer control activities are wholly dependent upon the development of a well-orchestrated cancer family history. Such a history will then enable the recognition of the cancer pattern, including its natural history within the pedigree, so that a hereditary cancer syndrome diagnosis might be possible. In addition, it will also facilitate identification of those individuals who warrant highly targeted surveillance, and who require genetic counseling and education about their cancer risk and its natural history to maximize compliance with the recommended surveillance and management strategies.

There are many hereditary disorders with premonitory phenotypic stigmata wherein knowledge of the family history can be applied immediately toward highly targeted cancer prevention strategies. Perhaps the best model is that of familial adenomatous polyposis (FAP), wherein recognition of the multiple adenomatous polyp phenotype, in concert with its autosomal dominant mode of genetic transmission, can lead to the identification of the risk status of that particular patient's parents, siblings, and/or progeny. These individuals will then merit intensive surveillance, and possibly prophylactic colectomy should the FAP phenotype be manifested.⁶ Having said this, in my own medical oncology practice I have seen many examples of patients at high risk for FAP presenting with metastatic

colorectal carcinoma. Soberingly, compilation of the family history, and acting upon this with appropriate prophylactic surgery in those patients with the FAP phenotype, could have proven lifesaving.

The more than 50 cancer-associated genodermatoses provide further examples of phenotypic signs (in this case cutaneous features) which could serve as beacons of cancer risk.¹⁰ For example, dysplastic nevi in autosomal dominantly inherited familial atypical multiple mole melanoma (FAMMM) syndrome, also referred to as the dysplastic nevus syndrome, provide strong indicators for cancer control measures through the recognition of these phenotypic stigmata.^{11,12} In the case of the multiple endocrine neoplasia (MEN) syndromes, there is a biomarker, namely, calcitonin excess; while in MEN-IIb, there are also cutaneous manifestations.¹³

The bulk of the more than 200 hereditary cancer and precancer syndromes lack premonitory phenotypic signs. In these disorders, the physician requires knowledge about the pattern of cancer transmission within the family pedigree. These include the several differing hereditary breast cancer syndromes, such as hereditary site-specific breast cancer,⁵ hereditary breast/ovarian carcinoma syndrome,^{14,15} and the recently described hereditary proneness to extraordinary early onset breast cancer.¹⁶⁻¹⁸ In the case of colorectal cancer, we have Lynch syndromes I and II.³

The general public—and their attorneys—have become increasingly aware of the importance of the cancer family history. Martin Flamm¹⁹ concluded that failure to diagnose cancer or to make such a diagnosis in a timely fashion was the leading allegation in negligence suits against physicians filed during the last decade. Malpractice attorneys began to file suits questioning the history-taking procedures used in the diagnostic approach. Recorded case law, although meager, would seem to support such a tactic.²⁰⁻²³ One decision held that a physician did not meet the standard of care in managing a patient with breast cancer when that clinician failed to do a proper genealogical survey.²⁴ Physicians would do well to heed such a judgment as a possible forerunner of a new type of negligence suit where any delay in the diagnosis of cancer, when there is a family history of that type of disease, is compensable.²⁵ Several additional suits have recently been filed alleging this same complaint, but as yet have not been fully litigated.

Finally, new advances in gene linkage will undoubtedly impact heavily on all facets of family history, including surveillance and management, psychological issues, and legal concerns. Specifically, in the case of early onset familial breast cancer, Hall et al²⁶ identified linkage of breast cancer susceptibility to the D17S74 locus (lod score 5.98) in early onset breast cancer prone families, and conversely they observed no linkage in those families showing late onset breast cancer. In our similar linkage study, three of five hereditary breast/ovarian carcinoma (HBOC) syndrome kindreds from the Creighton University Hereditary Breast Cancer (HBC) Registry showed positive linkage (lod score 4.39) to the same chromosome 17q locus, while negative lod scores were observed in the remaining two families. These data strongly support the identification of a breast cancer susceptibility locus on

17q12-q21 and are consistent with heterogeneity in HBC and HBOC. We anticipate further progress in molecular/genetic and gene linkage studies in cancer-prone families, thereby making it crucial that oncologists and family physicians become prepared for the application of this knowledge to the clinical practice setting.

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Geriatric oncology: Cervical cancer screening in elderly women

Persons 65 years of age and older are the fastest-growing segment of the United States population. The average person aged 65 can expect to live another 15 years and remain functionally independent for most of that time. The 75- and 85-year-olds have an average life expectancy of ten and six years, respectively, and will often function independently for most of that time. Thus, the greater portion of the elderly are active and functional and can benefit from health screening.¹⁻⁴

Cancer affects persons 65 years or older much more frequently than other age groups. The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program shows that more than 50% of all cancers occur in this age group. The data further indicate that the risk of developing cancer increases with the passage of each decade of life. In the 50- to 54-year age group, the average annual cancer incidence is 499.4/100,000. This rate more than doubles in the 60- to 64-year age group, to 1125.3/100,000. With increasing age, the rates escalate even more rapidly. United States mortality statistics for 1986 indicate that more than 65.7% of all cancer deaths occurred in persons 65 years of age or older.⁵

The screening of younger patients for cervical cancer by the use of the Papanicolaou (Pap) smear has greatly reduced the incidence of invasive disease and thereby increased survival and saved lives. There is strong evidence

that these screening procedures are underutilized by the elderly, particularly among minority groups. This is thought to have contributed to the relatively high incidence of invasive disease in these populations.^{2,3,5-7}

In the United States in 1988, approximately 7,000 deaths from cervical cancer occurred. The mortality rate among blacks was nearly 50% in excess of that of the white population. The incidence of invasive cervical cancer is approximately 12.4 per 100,000 women; the rate is higher in blacks and women of Hispanic origin. Mortality is also higher among elderly and poor women.

The principal risk factor for invasive disease from cervical cancer is the failure to receive routine Pap tests. Studies reveal that abnormal Pap smears are two to three times more likely to be found in previously unscreened women over the age of 65 compared with women under the age of 65. Studies also reveal that positive smears are more significant in older women because they are more often associated with invasive disease.⁵ In one study, carcinoma in situ was just as common in women over the age of 65 as in women under 65, but the rate of invasive carcinoma was four times higher than in the younger age group. In addition, there is a dramatic discrepancy in the stage of disease at diagnosis between older and younger women; 60% of the women in the youngest group were diagnosed with stage I disease compared to only 15% in the oldest age group. The incidence of stage III disease more than triples

from almost 9% in the youngest group to 29% in the oldest group.⁸⁻¹⁰

Recent data indicate that these older women have not been receiving routine screening for cervical cancer. A case control study from the Johns Hopkins University Hospital demonstrated a direct association between increasing age and the proportion of women who have never received a Pap test. Middle-aged and elderly women with cervical cancer were significantly less likely to have ever visited a gynecologist or to have reported any physician visit in the three years before diagnosis. In another case control study from Maryland, similar results were obtained. A steady increase is seen with age in the proportion of women who have never received a Pap test, and in the proportion of women who have not received a Pap test in many years. In the 65-plus age group, 38.9% have either never had a Papsmear or have not had one for at least five years. This study also emphasized that screening for cervical cancer is related to patterns of medical care use. Women who seek care from medical subspecialists, particularly gynecologists, are the most likely to receive routine, regular screening. The elderly who receive their care from general or family practitioners are less likely to be screened.^{3,5,9,11,12}

There are a number of barriers to adequate screening, generated by both physicians and patients. One important aspect of early detection is seeking procedures that identify illness in the absence of any symptoms. The elderly are often reluctant to accept examinations such as cervical cytology and breast self-examination.⁵ Attitudes, mistaken health beliefs, and a lack of information about these procedures and the potential benefits of early detection affect the likelihood that the elderly person will accept these procedures. Lack of knowledge about cancer risks, symptoms, and prevention are most prevalent among lower socioeconomic classes, minorities, and older adults.⁶ Patients' health beliefs also contribute to their attitudes about screening. It has been found that the more strongly a woman believes in the benefits of mammography, the more likely she is to have had a mammogram. With regard to cervical cancer screening, perceived risk and a belief in the efficacy of early detection and treatment all have been shown to play a motivational role.

The adequacy of social supports and the likelihood of early cancer detection have been explored in a study by Hibbard.¹³ He found that persons with a greater number of social ties were more likely to participate in preventive medical visits including Pap testing. These effects were most pronounced among persons over 65 years of age. Social supports may influence attitudes and encourage behavioral change.

Reluctance regarding early detection also reflects a general fear of dependence. Because of a lack of knowledge, women may not see the need for screening. In addition, many elderly women alter their pattern of care-seeking, particularly after menopause, and visit gynecologists less often. Data indicate that women are not likely to see a gynecologist after 55 years of age or to receive referrals for screening. This change greatly affects the likelihood of screening. Grover et al⁹ emphasized this point in a study of the Connecticut tumor registry. They found that delayed diagnoses of gynecologic tumors in elderly women were in

part due to the decreasing use of gynecologic examinations.

Physicians also contribute to the lack of screening among this population. The reasons include technical difficulties in performing an adequate cervical cancer smear for elderly women.^{3,5} If the physician is male, any gynecologic examination requires the presence of a female chaperone, which increases the time and personnel necessary to perform the screening.⁵ Another of the principal reasons general and family practitioners do not provide more cervical cancer screening is their belief that someone else is taking care of this need and that they may not have adequate expertise to provide it.⁵

Studies of physicians' observance of the American Cancer Society cancer screening guidelines reveal that obstetricians/gynecologists followed Pap test recommendations in 85% of patients in 1989. However, general practitioners and internists only followed them 54% and 40% of the time, respectively. These percentages are less than those reported in a 1984 survey.¹⁴

Elderly patients usually have regular and stable contact with medical personnel who could offer early detection. Between 83% and 85% of the elderly visit a physician at least once a year, and more than one half see a physician more than three times a year. Elderly patients usually present with multiple symptoms and chronic conditions, often overwhelming the physician, who leaves little time for screening.^{5,6} Physician encouragement of early detection methods appears to play an important role in patients' willingness to undergo screening. In one study, 93% of women reported that they would have a mammogram if their physician recommended it.¹⁵ Physician advice is clearly a predisposing factor for participation in cervical cancer screening.^{6,16,17} Women's attitudes toward their physicians and their perceptions of their physicians' communication abilities have also been shown to play a significant role in screening.¹⁸ However, an 1984 American Cancer Society survey indicated that only 11% of all physicians follow the American Cancer Society guidelines for mammography.¹⁹ In addition, while primary care practice is a logical place to provide cervical cancer screening, physicians often fail to take advantage of this opportunity.^{6,20,21}

There is substantial evidence that screening is beneficial in the elderly patient population as well as among younger women. In 1981, Holmes and Hearne¹⁰ demonstrated that with regard to cervical cancer, there was a highly significant positive relationship between advancing stage and advancing age. In addition, the stage of disease at the time of diagnosis was found to be an important determinant for treatment and survival. Goodwin et al²² also demonstrated similar findings. In their study, the most striking relationship between stage at diagnosis and age was found with cervical cancer. There was a dramatic increase with age in the percentage of cancers diagnosed at the regional and remote stages. This increase in the percentage of late stage cervical cancers with age remained after all in-situ cancers were eliminated from the analysis. More than 20% of the cervical cancers were diagnosed at the remote stage in women over 75 years of age. Fletcher¹¹ recently reported evidence that there is a potential for a 63% improvement in five-year mortality if screening were

to identify more cases of cervical cancer at an earlier stage in women over 65. Eddy²³ demonstrated that if a woman has undergone regular screening, the value of continuing screening beyond her mid-60s is fairly small. For women in their 60s who have not been screened in the previous dozen years, however, the value of screening might be considered sufficiently high to justify three or four examinations over the next ten years.

There are now differing screening recommendations put forth by various professional organizations. The American Cancer Society advocates that screening be performed between the ages of 20 and 65 every three years after two negative examinations one year apart.²⁴ The Canadian Task Force²⁵ and the British Society for Clinical Cytology²⁶ have similar recommendations, which include cessation of screening at ages 60 and 70, respectively. The American College of Obstetrics and Gynecology advocates annual and life-long screening.²⁷ These studies are based on the assumption that older patients have had screening. However, it has been amply demonstrated that this is often not the case. The position of the American Geriatrics Society is that Pap smear screening should be the responsibility of the patients' primary health care provider. Regular Pap smear screening should be performed at three-year intervals at least until the age of 70. A woman of any age who has never had a Pap smear or who does not have a history of Pap smears at recent routine intervals should be screened with at least two negative Pap smears one year apart. Departure from these recommendations is reasonable depending on individual circumstances, such as life expectancy and ability to undergo treatment if cancer is detected.³

A number of strategies have been used to increase adherence to screening guidelines.⁹ The didactic approach has been tried, but with limited success.²⁸ However, written instructions can have a more sustained impact on both knowledge and behavior.²⁹ Telephone counseling has been shown to be an extremely practical and cost effective method for cancer control, particularly smoking cessation. The use of mailed reminders and telephone counseling resulted in an 85% appointment keeping rate following colorectal cancer screening in one community. These techniques could be used for early detection programs to increase utilization of mammography and Pap tests and to enhance adherence to diagnostic follow-up once an abnormality is detected.⁶ The press and media have also played an increasingly active role in health education since they can reach people in the privacy of their own homes.

A variety of educational programs and practice interventions have been targeted toward physicians to increase currently low rates of early cancer detection practices. Cancer prevention education for medical students has been shown to produce long term increases in knowledge and improvements in attitudes and actual clinical practice of cancer screening.^{6,12,30,31}

The elderly, particularly members of minority groups, have a low rate of screening for cervical cancer. Further research is needed to expand our knowledge of adherence

to cancer control regimens and to develop methods to increase access for high risk populations.

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The potential use of tumor registry data in the recognition and prevention of hereditary and familial cancer

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ABSTRACT. The adequate collection and judicious use of family history data from cancer patients could aid in research studies, timely management of patients, and, potentially, eventual prevention of many forms of hereditary and familial cancer. The tumor registries of all 76 acute care nonpsychiatric hospitals in New York City were surveyed to determine if they contained data on family history of cancer. Only four of the 64 reporting hospitals recorded any of this information, and such information was not required by any accrediting agency. We cite examples of the use of tumor registry data, mainly from other countries, to locate families at risk for hereditary cancer. The addition of standardized questions about family history of cancer to tumor abstract forms is proposed, along with a linkage of tumor registry data with the services of the hospital genetics unit.

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More than 100 types of hereditary cancer have been identified, constituting 5% to 10% of the total cancer burden.¹ An additional 18% of cancers show familial clustering, suggesting the possible role of genetic factors.² This accumulating body of evidence supporting the aggregation of many types of cancers in families argues for the collection of as much data as possible from a proband about any relatives with cancer. With this information in hand, counseling and in some cases genetic screening can make family members aware of their increased risk for developing specific cancers, and may even allow for preventive action. Moreover, the increasing availability of gene-linked markers and growing knowledge of chromosomal abnormalities allow for identification of gene carriers for specific cancers well before the onset of disease, when some form of intervention could significantly reduce the risk. Conversely, appropriate history taking, counseling, and screening may relieve anxiety by identifying those family members who are definitely not at risk for a specific cancer. While careful follow-up and cancer education can be provided by a variety of health care professionals, clinical geneticists and genetic counselors are uniquely qualified to strike the precarious balance between imparting valuable, if troubling, information about risk to family members of a cancer patient, and minimizing the emotional trauma associated with receiving such information.³

Lynch et al² define an adequate family history for a patient with cancer as focusing on all first degree relatives (parents, siblings, and children) and selected second degree relatives, including both maternal and paternal grandparents, aunts, and uncles. Optimally, the treating physician should include in the medical history detailed questions about cancer in these family members. Often, however, these questions remain unasked because of the exigencies of medical practice or because of failure to realize their importance for cancer prevention.⁴ One study of existing charts in an oncology unit revealed that, in most cases, family history had been omitted altogether, incorrectly reported as negative, or not acted on.⁵

When adequate family history data have been obtained from a cancer patient, a logical place to look for the recording of this information is in tumor registry data abstracted from hospital records.⁶ Access to the tumor registry data would enable a hospital's genetics unit to provide appropriate counseling, health education, and screening tests, if available, to families at risk. On a larger scale, these data could be made available to regional cancer registries for research purposes or to any of the national registries for specific cancers, such as breast or ovarian cancer, familial adenomatous polyposis, or cancer family syndrome, for the purpose of monitoring and/or preventing further cancers in these families.

METHODS

In order to determine whether data on family history of cancer were being gathered in any systematic manner in New York City, our genetics unit undertook to survey all 76 acute care, nonpsychiatric hospitals to determine whether questions about family history of cancer were included on the tumor abstract forms currently used in these hospitals.

In addition, we interviewed several tumor registrars in New York City, as well as the Director of the New York State Cancer Registry, in order to understand how registries gather and process cancer information.

RESULTS

Sixty-four hospitals (84%) responded to our request for forms. These hospitals represented 92% of all inpatient hospital beds in New York City. Of these, 24 hospitals (37.5%) reported they had no tumor registry and did only the basic reporting required under New York State law. The mandated New York State abstract form does not ask about family history of cancer (William Burnett, MD, personal communication, April 4, 1990). The remaining 40 hospitals with active tumor registries sent us their tumor abstract forms; the resulting analysis for family history questions appears in Figure 1.

Of all 64 reporting hospitals, only four (6.2%) asked adequate

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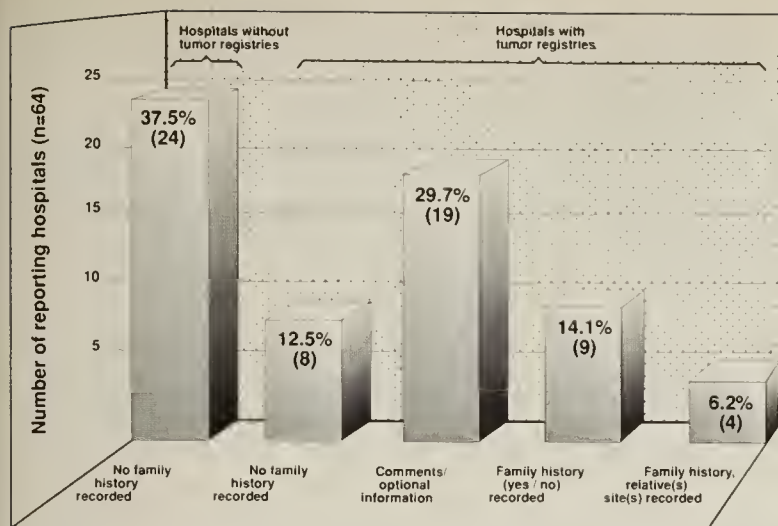


FIGURE 1. Recording of family history of cancer by tumor registries in 64 New York City hospitals, June 1990.

questions about the site(s) of cancer and the specific relative(s) in whom it was found. Nine other hospitals (14.1%) asked only whether or not there was cancer in a family member, and 19 hospitals (29.7%) used forms with a box labeled "Comments" or "Optional Information," most without any suggestion about what optional information to record. Forms used by the remaining eight hospitals (12.5%) had no questions at all about cancer in family members and no space for recording optional information.

According to interviews with several tumor registrars, the forms, usually abstracted from hospital records within six months of diagnosis, are used to generate monthly reports and some annual patient care evaluation studies necessary for the accreditation of the registry by the American College of Surgeons. The reports are kept on file in the hospital and are used for in-hospital studies of cancer occurrence and treatment of outcomes (Elaine Arden, RRA, CTR, personal communication, March 26, 1990). As a general rule, referrals are not made from the hospital's tumor registry to any of the specialized familial cancer registries. This is because tumor registries serve a data gathering function and usually have limited contact with patients or their families (Rachel G. Fruchter, PhD, personal communication, March 26, 1990).

DISCUSSION

The pattern that emerges from examining the tumor abstract forms used in New York City hospitals is that little or no information about a family history of cancer is gathered in a systematic way. Reporting on family history of cancer is not required, either by the New York State Cancer Registry (William Burnett, MD, personal communication, April 4, 1990) or by the American College of Surgeons (Elaine Arden, RRA, CTR, personal communication, March 26, 1990), which provides model forms for hospitals to follow. In the two largest of the four hospitals with adequate family history questions on their forms, there is no formalized reporting mechanism linking the tumor registries with the specialized registries for familial or hereditary cancers or with genetics units in the city's hospitals (Ruben Rodriguez, CTR, Barbara Francois, CTR, personal communication, April 23, 1990). This information was unavailable from the other two hospitals.

Broadly speaking, there are two types of cancer registries. Population-based registries use the entire population (usually of a state) as a denominator and generate epidemiologic data (cancer incidence, prevalence, and death rates) and time trend studies. Cancer registration in the United States is not universally required by all states, and

registries, where they exist, are not always population-based (William Burnett, MD, personal communication, April 4, 1990). Physician-based registries exist to serve the needs of cancer patients and their families through counseling and assessment of their cancer risk.⁷ Referrals from population-based registries to physician-based registries are rare, largely because of concerns about privacy and confidentiality.

Familial cancer registries in the United States are generally physician-based, with referrals coming from treating physicians and surgeons and, in some cases, from the families themselves. Examples of these registries include the Familial Ovarian Cancer Registry in Buffalo, New York, and the Hereditary Cancer Institute in Omaha, Nebraska. Several examples exist in other countries (Iceland and The Netherlands, for example), in which population-based registries provide their data, with appropriate safeguards, on a continuing basis to registries for specific familial or hereditary cancers.^{8,9} In contrast, the physician-based registries in the United States have no regular source of referrals and must rely on advertising and on the awareness of individual physicians and the public about the familial or hereditary nature of a particular cancer.

New knowledge about DNA and biochemical markers as well as chromosomal abnormalities, paired with accurate family history data, can now identify family members at risk for specific cancers. A recent German study of six families with retinoblastoma affecting one or more members used pedigree analysis together with DNA markers to find currently unaffected individuals carrying a genetic risk for later development of the disease.¹⁰ In familial adenomatous polyposis, an autosomal dominant disorder recently mapped to a region of chromosome 5, 75–80% of asymptomatic gene carriers can now be identified at a much earlier age by the presence of congenital hypertrophy of the retinal pigment epithelium.¹¹

In many cancers, however, obtaining accurate family history data may be the only means currently available to identify family members at risk. In hereditary nonpolyposis colon cancer, early age of onset, predominance of tumors in the proximal colon, and other clinical and family history data may be the only clues to distinguish these cancers from the far less aggressive sporadic colon cancers.¹² Likewise, in hereditary breast cancer transmitted in an autosomal dominant pattern, only early onset and the increased risk to the contralateral breast differentiate it from sporadic forms.¹³ Though it accounts for 9% of all cases of breast cancers and exposes female first degree relatives to a 50% risk, the hereditary form is often missed because an accurate and focused family history is not taken.⁴ Family members at high risk (50%) for hereditary ovarian cancer can be identified simply because of their position in the pedigree. For this reason, Lynch et al¹⁴ and Piver et al¹⁵ stress the importance of taking an adequate family history to establish an accurate pedigree of all cases of ovarian and other cancers within a family, so that the family members may benefit from cancer education, surveillance, and in some cases, prophylactic oophorectomy.¹⁴

Even in the face of concern about a cancer risk to family members, physicians may hesitate to refer a family for genetic counseling in the belief that it will cause undue

anxiety.⁵ After genetic counseling, however, there is often relief from the burden of uncertainty and misinformation, as well as the hope of prevention through improved surveillance and screening programs.¹⁶ Familial cancer registries have reported that probands and their families have often already considered genetic factors as an important etiologic factor.¹⁷

We propose a mechanism that would allow for the identification of some families who would benefit from cancer genetic counseling. The addition of standardized items regarding family history of cancer to the tumor abstract forms in all New York City hospitals would provide a simple means of identifying the families at risk. The items would include information about whether a first or second degree relative of a cancer patient had cancer, the exact pedigree relationship, the site(s), histologic type (if known), age of onset, and whether genetic counseling was suggested or obtained. After receiving this information periodically from the tumor registry in a manner that safeguards the patient's privacy, the hospital's genetics unit would determine which families might be targeted for counseling, based on their genetic risk. Family members at risk could then be offered available screening tests for the cancer or cancers in question. This linkage of tumor registry data with the services of the in-hospital genetics unit would be especially beneficial to families seen in the clinic, who might have limited access to these services.

Such a system would also provide a means to recall families at risk, should research make new prevention strategies available for a particular familial or hereditary cancer. Communication with a service within hospitals would increase physician awareness of the need to record a detailed family history and might result in more referrals to specialized registries for hereditary cancer.

In summary, we believe that the simple mechanism we have proposed would serve to increase the opportunities

for recognizing and alleviating the burden of familial and hereditary cancer.

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An epidemiologic study of Pap screening histories in women with invasive carcinomas of the uterine cervix

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ABSTRACT. The present study was designed to determine the Pap screening histories of 261 women, ages 20 through 69 years, who were diagnosed with an invasive carcinoma of the uterine cervix. Women who were residents of New York State, exclusive of New York City, and who received a diagnosis between July 1983 and September 1985, were select-

ed for this study. Fifty-four percent of the patients had not received at least one Pap test within three years prior to diagnosis. Women who had not received a prior Pap smear tended to be older, less sexually active, less well educated, and to have more extensive disease at the time of diagnosis than women who had received cytologic examinations. The present study results, coupled to findings of previous reports, demonstrate the need for an intensified effort to insure that all women have access to quality Pap screening services. Particular emphasis needs to be placed on reaching older women who are less likely than younger ones to receive periodic Pap screening. Physicians need to routinely offer older

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patients who present with nongynecologic conditions the opportunity of receiving cytologic testing.

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Mortality rates for carcinomas of the uterine cervix have declined by 79% in New York State between 1950 and 1987.¹ Despite the lack of definitive evidence linking the Pap smear with decreases in cervical cancer mortality, suggestive evidence supporting this has been produced from an array of population-based studies.² An association between the use of the Pap smear and cervical cancer mortality is supported by differences in cervical cancer mortality rates among screened and unscreened women from the same population. Correlations between screening and cervical cancer mortality rates in different populations, and time trend analyses showing steady declines in cervical cancer mortality beginning approximately ten years after the introduction of cytologic screening, provide further support for this association. Despite significant declines in cervical cancer mortality and the current high usage rates for cervical cytologic testing in New York State,³ continued efforts are needed to prevent the nearly 340 deaths due to this disease that still occur among New York State women each year.¹ The current study was designed to determine the Pap screening histories of women reported to the New York State Cancer Registry with an invasive carcinoma of the uterine cervix.

PATIENTS AND METHODS

Women diagnosed with an invasive carcinoma of the uterine cervix between July 1983 and September 1985, and reported to the New York State Cancer Registry by a hospital located in the study area (New York State, exclusive of New York City) were eligible for selection as subjects. In addition, all subjects had to be 20 through 69 years of age at the time of diagnosis.

A total of 1,033 eligible cervical cancer patients were diagnosed during the study period, but were reported to the New York State Cancer Registry over a longer time period. In order to minimize losses due to mortality, eligible patients were identified by Health Department staff from incoming case reports in the order they were received by the registry. Five hundred eighteen (518) eligible patients were identified in this manner, representing 50.1% of the total cohort of patients eventually reported to the registry. Interviews were conducted with 261 patients (50.4%). There were several major reasons for not conducting interviews with the remaining 257 patients: failure to obtain physician clearance for an interview (36.2%); patient refusals (15.9%); patient deceased (18.7%); and other miscellaneous reasons (28.2%) including third-party refusals, no phone, English not spoken, and patient under psychiatric care, and in the opinion of the physician unable to undergo an interview.

A standard form was used to gather selected sociodemographic, clinical, and pathologic data from each patient's hospital record. In addition, representative slides of the initial biopsy material were obtained from hospitals for review and diagnostic confirmation.

Physicians of record were contacted by mail to obtain permission to contact their patients. Once permission was granted, each woman was sent a letter explaining the study and inviting her to participate. Each woman was then telephoned by the study staff and, if she agreed to participate, a 20-minute interview was conducted. The interviewer collected information on sociodemographic characteristics; a history of symptoms noted prior to diagnosis; and menstrual, contraceptive, reproductive, and sexual histories. More specifically, questions were asked regarding race, age, income, education, episodes of vaginal bleeding, age at first coitus, and lifetime number of sexual partners. Data collection

and interviewing were performed by experienced staff who had conducted interviews for previous epidemiologic studies.

The patients were also asked about Pap smears performed during the three-year period prior to the diagnosis of their invasive cervical cancer. The three-year period was chosen because New York State Public Health Law requires laboratories performing cervical cytology to maintain negative slides for a period of only three years. Women who reported having a Pap smear within three years of diagnosis were asked to provide the date of each Pap smear and the name of the physician who collected the specimen. The women were also asked to indicate whether the Pap smear leading to their diagnosis was taken because of specific symptoms or as part of a routine gynecologic examination. Pap smears that led to the initial diagnosis of invasive cervical cancer were not included in the analysis. These Pap smears were eliminated in order to focus the current analysis on each patient's screening history prior to diagnosis. The patients' physicians were then contacted to obtain confirmation of the Pap smear history provided by the patient.

Standard contingency table⁴ analysis was used to determine differences between invasive cervical cancer patients who reported and who did not report at least one screening Pap smear within three years of diagnosis. Cross-tabulations of previous Pap smear history by various epidemiologic variables were accomplished with the personal computer version of the SAS statistical package.⁵ Chi-square statistics, including trend tests, were calculated using the statistical package EPISTAT.⁶

The survival experience of patients with and without previous Pap smears was determined by searching the death certificate files maintained by the New York State Office of Vital Records. Patients not located in the death certificate files for the period 1983 through 1989 were assumed to be alive through four years of follow-up. Relative survival rates were calculated through four years of follow-up time by dividing the observed survival rate by the expected survival rate for the study population. The relative survival rate allows all causes of death to be included in the analysis, while adjusting the final results for the effects of mortality due to causes other than cervical cancer.⁷ The methods suggested by Ederer et al⁷ were used to calculate the expected, observed, and relative survival rates. Confidence limits were calculated for the relative survival rates utilizing the tables compiled by Ederer.⁸

RESULTS

The 261 interviewed patients were compared to the 1,033 eligible patients diagnosed during the study period and eventually reported to the New York State Cancer Registry. The interviewed patients were similar to the registry population in terms of age ($\chi^2 = 13.51$, degrees of freedom (df) = 9, $p = 0.14$) and race ($\chi^2 = 2.74$, df = 2, $p = 0.25$). The interviewed patients were more likely to be diagnosed with localized disease (61% vs 55%, $\chi^2 = 5.38$, df = 2, $p = 0.07$) when compared to the registry population.

One hundred and forty-one (54%) of the 261 women studied reported that they had not had a Pap smear within three years of their date of diagnosis. A total of 119 (46%) invasive cervical cancer patients gave a history of having received one or more Pap smears within three years of diagnosis. Thirty-two of these women did not sign a medical release form, and their cytologic information could not be requested from the attending physician. For an additional 28 women, the attending physician was unable to confirm that a Pap smear had been performed within the previous three years. The remaining 59 women had their Pap smear histories confirmed.

The distribution of several established risk factors for cervical cancer was examined among women with and without a Pap smear history. These variables included age, income, education, age at first coitus, and lifetime number of sexual partners (Table I). The small number of single and nonwhite patients did not permit analysis by race or marital status. The probability that a woman received one or more previous Pap smears was most strongly related to age at diagnosis (χ^2 linear trend = 37.20, df = 1, $p = <10^{-6}$). Women who reported having a Pap smear within three years of diagnosis were sig-

nificantly younger than women who had not had a Pap smear.

Although no significant differences were noted in relation to income (χ^2 linear trend = 0.26, df = 1, p = 0.61), women who had not received a Pap smear tended to have less schooling than women who had received uterine cytologic examinations (χ^2 linear trend = 4.18, df = 1, p = 0.04). Women with a history of previous Pap smears also tended to be more sexually active than women without a previous Pap smear. These women were more likely to have been less than 20 years of age at first coitus (χ^2 = 3.28, df = 1, p = 0.07) and to have had five or more sexual partners (χ^2 = 10.52, df = 1, p = 0.001). These findings were maintained even after stratifying by age at diagnosis. These sociodemographic data are presented in graphic form in Figures 1 and 2.

One hundred and ninety (73%) invasive cervical cancer patients had their disease diagnosed because of an ongoing gynecologic problem. The most commonly reported problem (69%) was a history of vaginal bleeding. However, among women with a Pap smear history, 46 (39%) were diagnosed during a routine visit, compared to only 25 (18%) women without a Pap smear history.

Women who reported having a Pap smear were found to have less extensive disease at the time of diagnosis when compared to women who had not received uterine cytologic examinations (Table II). Seventy-seven percent of women with a Pap smear history were diagnosed with localized disease, compared to only 58% of invasive cervical cancer patients without a previous Pap smear. These differences were found to be statistically significant (χ^2 = 8.40, df = 1, p = 0.004).

Because age has been shown to be related to stage at diagnosis and

TABLE I. Invasive Cancers of the Uterine Cervix: History of Receiving a Pap Test Within Three Years of Diagnosis by Selected Risk Factors

Risk Factor	Previous Pap Smear History	
	Yes	No
Age (yr)		
20-34	35 (29.4)*	4 (2.8)
35-44	33 (27.7)	35 (24.7)
45-54	30 (25.2)	38 (26.8)
55-64	16 (13.5)	51 (35.9)
65+	5 (4.2)	14 (9.9)
Total	119†	142
χ^2 linear trend = 37.20, df = 1, p = <10 ⁻⁶		
Education		
Less than high school	28 (23.5)	47 (33.3)
High school graduate	51 (42.9)	60 (42.6)
More than high school	40 (33.6)	34 (24.1)
Total	119	141
χ^2 linear trend = 4.18, df = 1, p = 0.04		
Income		
Less than \$10,000	40 (34.5)	50 (37.6)
\$10,000-\$25,000	44 (37.9)	49 (36.8)
More than \$25,000	32 (27.6)	34 (25.6)
Total	116	133
χ^2 linear trend = 0.26, df = 1, p = 0.61		
Age at first coitus		
Less than 20 years of age	83 (72.2)	81 (60.4)
Greater than or equal to 20 years of age	32 (27.8)	53 (39.6)
Total	115	134
χ^2 = 3.28, df = 1, p = 0.07		
Number of sexual partners		
Less than 5	72 (65.5)	112 (84.2)
Greater than or equal to 5	38 (34.5)	21 (15.8)
Total	110	133
χ^2 = 10.52, df = 1, p = 0.001		

* Percent.

† Totals for each risk factor may differ due to differential response rates.

‡ df, degrees of freedom.

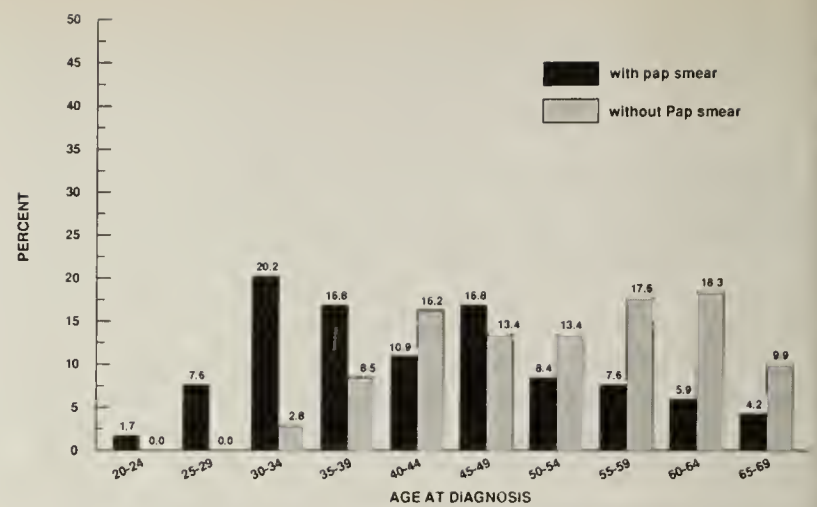


FIGURE 1. Percent distribution of invasive cancer of the uterine cervix by age and history of Pap smear prior to diagnosis.

prior Pap history, the relationship between Pap history and stage was examined for different age groups (Table III). Among patients less than 50 years of age at the time of diagnosis, women with previous Pap smears were more frequently diagnosed with localized disease than were women without Pap histories (χ^2 = 5.93, df = 1, p = 0.015). A similar pattern was observed for women age 50 years and older, but the differences were not statistically significant.

Further analysis compared the four-year survival experience of women with and without previous Pap histories (Table IV). Women with a Pap history tended to have more favorable relative survival rates (85.6%) than women without a Pap history (77.1%). The direction of these findings is consistent with the stage at diagnosis patterns observed in these two groups of patients. However, the 95% confidence intervals for these survival rates do overlap, and the possibility that these differences may be due to chance cannot be ruled out.

The sociodemographic and "stage at diagnosis" results were even more apparent when comparing those women with a confirmed Pap smear history to those without a Pap smear history (Fig 3). The women with a self-reported Pap smear history that was not confirmed tended to be intermediary to the other two groups.

The hospital records of 50 patients with confirmed Pap smear histories were reviewed. For nine patients, copies of the hospital records were not complete enough for review. Of the reviewed records, 14 had Class I (negative) cytologic results and no definable symptoms during the three years prior to diagnosis. These women were eventually diagnosed with invasive cervical cancer when a positive Pap smear was reported or symptoms of short duration led to a biopsy. The time interval between the last normal Pap smear and the date of diagnosis ranged from 8 to 31 months, with a mean of 15 months. The remaining 36 patients (72%) had been under medical surveillance because of a history of mild, moderate, or severe dysplasia, or because the patient had experienced symptoms (eg, cervicitis, vagi-

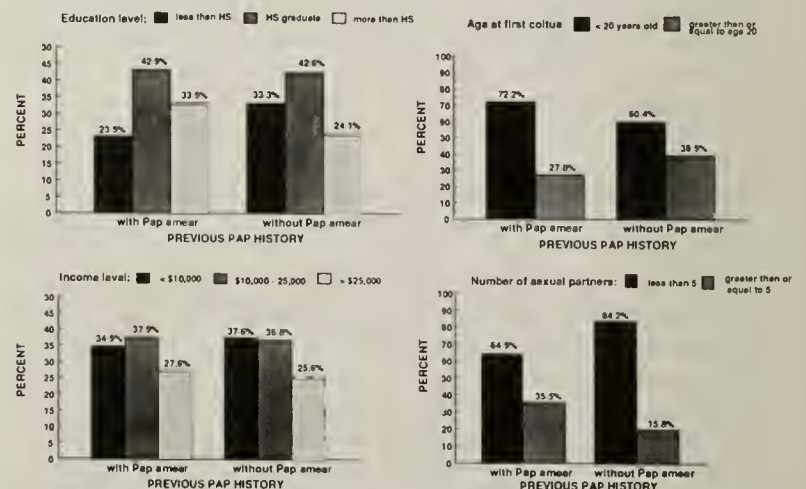


FIGURE 2. Education, income, age at first coitus, and number of sexual partners among women with cancer of the uterine cervix by history of Pap smear prior to diagnosis.

TABLE II. Invasive Cancers of the Uterine Cervix: History of Receiving a Pap Test Within Three Years of Diagnosis by Stage at Diagnosis*

Stage of Disease	Previous Pap Smear History	
	Yes	No
Localized disease	86 (76.8) [†]	74 (58.3)
Regional spread	22 (19.6)	44 (34.6)
Distant metastasis	4 (3.6)	9 (7.1)
Unknown	7	15

* χ^2 (localized stage vs regional spread + distant metastasis) = 8.40, df = 1, p = 0.004.

[†] Percent.

nal discharge, post-coital bleeding, menstrual irregularities, etc). A number of women with dysplasia or cervicitis were treated with conization or cryosurgery. Because many of these women may have been treated on an outpatient basis, it is not possible to assess the full extent of the therapies used in these patients from the medical histories given in the inpatient records alone. These women eventually underwent biopsies and received a diagnosis of invasive cervical cancer when a Pap smear suggested the presence of frankly malignant disease, or when the patient's symptoms continued, returned, or increased in intensity.

DISCUSSION

The current study suggests that a majority of women diagnosed with invasive carcinoma of the uterine cervix do not receive routine Pap smears. Patients who had not received at least one Pap smear within three years of diagnosis tended to have more extensive disease and poorer survival rates when compared with women who had received uterine cytologic examinations. Women who had not received a Pap test also tended to be less sexually active, more poorly educated, and older than women who had received cytologic testing. The strong age effect observed in the present study is consistent with findings from previous studies⁹⁻¹¹ and population-based surveys, which show decreased annual or triennial Pap screening rates in older women.^{3,12-16} Previous studies^{9,10} have also shown that medical care factors, including recent outpatient visits and lifetime use of an obstetrician-gynecologist, increase the probability that women continue to receive routine Pap testing even after they are past the childbearing period. The tendency for better educated, more sexually active women to have had previous Pap tests is also consistent

TABLE III. Invasive Cancers of the Uterine Cervix: History of Receiving a Pap Test Within Three Years of Diagnosis by Age and Stage of Disease at Diagnosis

Variables	Previous Pap Smear History	
	Yes	No
Age and stage at diagnosis		
<50 years		
Localized disease	66 (80.5)*	31 (59.6)
Regional spread or metastasis	16 (19.5)	21 (40.4)
Unknown	4	3
$\chi^2 = 5.93$, df = 1, $p = 0.015$		
≥ 50 years		
Localized disease	20 (66.7)	43 (57.3)
Regional spread or metastasis	10 (33.3)	32 (42.6)
Unknown	3	12
$\chi^2 = 0.44$, df = 1, $p = 0.51$		

* Percent.

TABLE IV. Relative Survival Rates (Four Years) for Invasive Cancers of the Uterine Cervix by History of Receiving a Pap Test Within Three Years of Diagnosis

Previous Pap Smear History	Number of Patients	Relative Survival Rate	95% Confidence Interval
Yes	119	85.6%	78.3-91.5
No	142	77.1%	69.3-84.9

with increased utilization of gynecologic services such as family planning.

The data also show that some women will go on to develop an invasive carcinoma despite receiving one or more Pap smears or continuing medical surveillance for gynecologic symptoms. Based on a retrospective review of medical records, it was not possible to differentiate the factors that might be most strongly associated with the failure to prevent the development of these invasive lesions. The current data suggest, however, that this problem occurs more frequently than might be appreciated and indicates the need for additional research to assess the role of clinical and laboratory factors.

Despite the overall high rates of Pap screening in New York State,³ additional efforts are needed to insure that all women have access to quality screening. Data from the New York State Cancer Registry show high incidence rates for invasive cancer of the uterine cervix among minority women, women from lower socioeconomic levels, and rural populations, and women over 40 years of age.¹ Fruchter et al,¹⁷ in a study of low income women diagnosed with invasive cancer of the uterine cervix, reported that 73% of unscreened women had received some ambulatory care within five years of their cervical cancer diagnosis, while 41% received regular ambulatory care for chronic conditions. They also reported that 16% of unscreened women had been hospitalized at least once. The findings reported by Fruchter et al¹⁷ show that the regular medical care practices of high risk populations present many opportunities for diagnosing cervical cancer in an early clinical stage, opportunities that are currently being missed. Similar findings have been reported by other authors.^{18,19} Medical practitioners need to be alert to opportunities for providing Pap screening services to these high

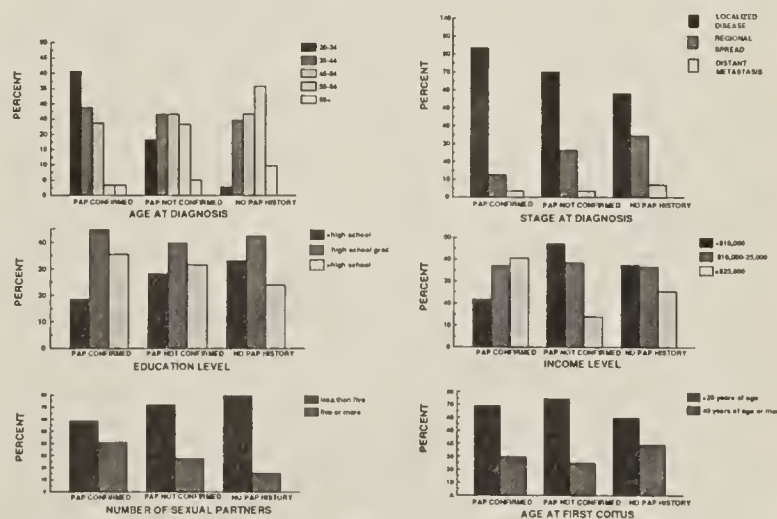


FIGURE 3. Invasive cancers of the uterine cervix, history of receiving a Pap smear within three years of diagnosis by selected risk factors and confirmation status.

risk and overlooked populations.

Whenever feasible, routine Pap screening should be integrated into the standard patient management procedures of the physician's medical practice. Clinic staff need to be reminded of the need to offer Pap testing to high risk women even in the absence of a perceived gynecologic problem. Specific methods for increasing Pap screening levels need to be tailored to meet the unique characteristics of the population served by the individual medical practice and need to take into account the organizational structure of each service component.

Findings from previous studies also demonstrate a continuing need to encourage the use of established techniques for collecting cytologic specimens and preparing slides. Screening for cervical cancer with the Pap smear is a far more complex process than many physicians and health care providers appreciate. In order to properly perform a cervical Pap smear, the patient must be properly positioned, there must be very good lighting, a proper sized spatula is required, and the cervix must be fully exposed and visualized. Poorly trained and inexperienced house staff cannot perform this test well.²⁰⁻²²

There are multiple devices available to obtain a smear. These include the Ayre spatula, modified spatulas (wood or plastic), cotton tip applicators, pipettes, cytobrushes, tampons, glass aspirators, and wash techniques.^{20,23,24} The most common device is a spatula and/or cotton tip applicator. An Ayre's type spatula (preferably the extended tip type), provides a firm circumferential scrape of the ectocervix. This should be followed by or preceded by the cytobrush rather than the cotton tip applicator.²³⁻³¹ The cytobrush has been shown to decrease the chance of inadequate smears and increase the yield of endocervical cells.²⁶ The cytobrush may cause some bleeding, but it is rarely of significance and usually does not interfere with slide interpretation. In postmenopausal women, a vaginal pool sampling, using a spatula or a pipette aspiration device, can increase the accuracy for screening for endometrial cancer and hyperplasia.^{20,21,32}

It is very important that the prepared slides be immediately fixed in 70% to 95% alcohol or fixed with the commercial slide spray fixatives.²⁰⁻²² Hair sprays should not be used.³³ Air drying will cause artifacts that will make slide interpretation inaccurate and therefore add to the laboratory error rate.²⁰⁻²² The physician should have trained personnel helping with the collection, spraying, and preparation of the slides.

Accuracy can be improved by using more than one slide. Three slides taken at the same time^{20,34-36} should clearly identify the ectocervix, endocervix, and vaginal pool sample.

Other factors that may help decrease false negative results include educating the patient not to douche and to refrain from intercourse one to two days before the examination, as well as taking the smear in the second half of the menstrual cycle.

The present study results, and findings from previous reports, demonstrate the need for an intensified effort to insure that all women have access to quality Pap screening services. Particular emphasis is needed on reaching older women who are less likely than younger women to receive periodic Pap screening. Physicians should offer older pa-

tients who present with nongynecologic conditions the opportunity to receive cytologic testing.

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A physicians' guide to quality review

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Medical record documentation can be a baffling process if the correct procedure is not understood and routinely used. Likewise, the peer review process is sometimes viewed by physicians as a mystery, explained or unveiled only when a problem surfaces and when an immediate response or corrective action is required.

The following is intended to shed light on both the best way to document medical records and on the peer review system as administered in the state of New York by Island Peer Review Organization, Inc (IPRO).

A BRIEF HISTORY OF IPRO

The role of assuring accessible and quality care to the medically indigent and Medicare beneficiaries in New York was awarded to IPRO in December 1989, based on two separate competitive bids to the New York State Department of Health and the US Department of Health and Human Services. The Medicare review program expects an annual volume of 240,000 preadmission/preprocedure and 215,000 retrospective medical chart reviews. This program now conducts approximately 40,000 telephone preadmission and 100,000 chart reviews.

IPRO is one of the two largest independent peer review organizations in the United States, with more than 15 years of continuous utilization and quality review experience on behalf of national and New York State clients. Each of the more than 300 hospitals throughout New York State is visited by IPRO review staff on a regular basis. IPRO processes over 1,200,000 hospital claims annually in its in-house data system, with approximately 25-35% of the cases selected for chart review.

IPRO has six field offices located throughout New York State: in Lake Success, Albany, New Hartford, Syracuse, Buffalo, and Rochester. These offices are fully staffed and carry out assignments to conduct reviews at all hospitals and health care facilities in New York State. Field offices are linked to corporate headquarters in Rego Park, Queens, by computer lines which provide instantaneous review updating and data transfer. All corporate policies regarding planning, review procedures, criteria, training, personnel, budgeting, finance, and contracting are managed by the staff in the corporate headquarters office.

IPRO's main computer systems and professional analysts are also located at corporate headquarters. Special projects, research projects, and sensitive quality reviews

are conducted at the Queens location. Due to the special nature of the information IPRO collects, reviews, and stores in the course of conducting private and governmental review programs, strict confidentiality measures are followed by all staff.

IPRO's board of directors comprises practicing physicians and hospital, consumer, and state medical society representatives. Under the Medicare and Medicaid review activities, in addition to the quality review process and interventions, ongoing improvement in quality of care is IPRO's main objective. It is the belief of the board of directors that the best mechanism to use to achieve that goal is education.

THE QUALITY REVIEW PROCESS

Charts for review are selected by IPRO from the fiscal intermediary. A review worksheet is printed for each case from the IPRO computer system. IPRO's Program Review Analysts (PRAs), all registered nurses, review the selected charts in the hospital or at an IPRO office to determine whether a potential utilization and/or quality issue exists. If a potential issue is identified, the chart is immediately referred to a physician consultant (PC). This physician, following his or her own review of the chart, will make an independent decision on the case. If the PC disagrees with the PRA, the case is closed. If the two agree, IPRO sends a pre-denial notification to the source (ie, the hospital and/or physician central to the case).

The pre-denial notification requests the physician to address the comments and questions identified by the PC.

Applications for physician consultants are solicited from practicing physicians who maintain active hospital privileges in the state of New York. The Health Care Financing Administration (HCFA) regulations exclude radiologists, pathologists, and emergency room physicians, except as consultants for specific cases. The application is processed by the Office of the Vice President for Medical Affairs at IPRO, who makes a final determination regarding the type of review the new PC will perform. All new PCs are required to attend an orientation program. All PCs at IPRO are board certified or qualified. In addition, a roster of special consultants is available on a case-by-case basis in the event that a disagreement surfaces.

The hospital or physician is allowed 30 days under HCFA regulations to respond to the pre-denial notice, which is then sent to a second physician consultant, usually within the same specialty and working in a similar setting as the physician under review. Should the second PC agree with the hospital and/or attending physician's re-

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sponse, the case is closed. If not, a final determination notice is sent to the same hospital or physician.

The final determination notice specifies a full description of the confirmed quality problem in clear and sufficient detail so as to prevent such problems in the future; the acceptable medical practice(s) that should have been performed in the case; and the severity level of the quality problem.

Each case reviewed by the IPRO is screened for the following: quality review (including HCFA generic screens); discharge review; admission review; invasive procedure review; DRG validation (coding validation for non-PPS and ambulatory surgery), including physician attestation review; coverage review; waiver of liability applicable to denials.

CASES SELECTED FOR REVIEW

According to the Medicare Third Scope of Work, the following cases are selected by IPRO for review. Each state in the country has nearly identical requirements:

- Random sample of 3%
- 50% of transfers from PPS hospital to PPS hospital
- Transfer from PPS hospital to exempt psychiatric unit
 - 100% with organic brain conditions
 - 100% without valid psychiatric diagnosis
 - 10% with valid psychiatric diagnosis
- 25% of PPS hospital readmissions
- 20% of intervening care
- Focused DRGs
 - 35% of DRG 462 (rehabilitation)
 - 50% of DRG 468 (extensive OR procedure unrelated to principal diagnosis)
 - 100% of:
 - DRG 385 (neonates, died or transferred to another acute care facility)
 - 386 (extreme immaturity or respiratory distress syndrome neonate)
 - 387 (prematurity with major problems)
 - 388 (prematurity *without* major problems)
 - 389 (full-term neonate with major problems)
 - 390 (neonate with other significant problems)
 - 391 (normal newborn)
 - 472 (extensive burns with OR procedure)
 - 474 (respiratory system diagnosis with tracheostomy)
 - 475 (respiratory system diagnosis with ventilator)
- 25% of day outliers
- 25% of cost outliers
- Medicare code editor 100%
- 100% of hospital adjustments to higher-weighted DRG
- Non-covered admissions
- Fiscal intermediary and HCFA regional office referrals

- Ambulatory surgery
- Sample selection—5% random sample by facility
- The review process examines:
 1. Quality of care
 2. Medical coding techniques
 3. Appropriateness of procedure
 4. Waiver of liability
 5. Ancillary services

STATEWIDE QUALITY ASSURANCE COMMITTEE

The three quality assurance (QA) committees in the state function independently, are staffed by IPRO's medical directors, and provide the peer review process with broad geographic and medical specialty representation. The Upstate QA committee is chaired by Bruce McDonald, MD, and staffed by Eugene Beltrami, MD; the Metropolitan QA committee, chaired by Douglas Prisco, MD, is staffed by Monte Malach, MD; and the Downstate QA committee, chaired by Daniel Sherber, MD, is staffed by Monte Malach, MD. In addition, Frank Inquinta, MD, is the Medical Director for Beneficiary Outreach and Central Quality Review. Approximately 22–26 physician members, including hospital representatives, sit on each QA committee. Level III Medicare cases are generally referred to these committees for discussion and further evaluation.

AN EXAMPLE OF A FREQUENT QUALITY ISSUE

Following is an example of the type of cases now being examined by IPRO's medical directors and/or quality assurance committees:

A 73-year-old patient residing in a nursing home was scheduled for ambulatory cataract surgery on a specified day. Because of emergencies at the community hospital that day, the surgery was cancelled and rescheduled for seven days later. When the patient was admitted to the ambulatory surgical unit at a later date, he was taken to the operating room after a brief history and a physical examination completed by the house staff. Because of the patient's age an EKG was performed and a chest film was taken. Following cataract surgery, the patient was brought back to the unit. A few hours later, congestive heart failure developed and, despite interventions by a cardiologist and pulmonologist, the patient subsequently died.

Upon reviewing the chart, IPRO's PC found the following quality issues. The patient went to the OR without medical clearance, despite the fact that his EKG was abnormal and his medical history included unstable angina and hypertension. Further, the patient was admitted under the care of his internist whom he had never met while in the hospital.

A pre-denial notice went to the internist, whose name was obtained from the chart. The internist notified IPRO that he was never advised of the patient's admission, did not clear the patient for surgery, and was called only after the patient was critically ill in the ambulatory unit and subsequently transferred to the coronary care unit (CCU).

The attending anesthesiologist asserted that he had tried unsuccessfully to get in touch with the patient's phy-

sician and had decided to clear the patient himself as the ophthalmologist would be unavailable the next day.

The patient's internist is not responsible; he did not admit the patient, nor were there any indications that he was called. The surgeon should not have proceeded with the surgery without clearance, and the anesthesiologist should not have cleared a patient who had a documented history of unstable angina with hypertension. The hospital should not have admitted a patient without notification from the attending physician. These are all quality issues relative to the surgeon, the anesthesiologist, and the hospital.

NEW SERIES AT IPRO

IPRO's Education Committee, under the chairmanship of Stephen Scheidt, MD, is developing education courses and is in the process of approving existing educational lectures in various hospitals. The medical director and/or the quality assurance committee will be guided by the education committee's recommendations in assigning education intervention.

The following chart documentation suggestions were developed and recommended to this committee for distribution to all physicians and hospitals. They assist the physician in preparing a record which accurately and adequately documents the care rendered to a patient in the hospital:

1. Complete history and physical examination, including baseline laboratory values, Pap smear, breast examination, and rectal examination. A provisional diagnosis must be documented.
2. Daily progress notes that reflect findings, assessment, and plan of care are required. Avoid use of such phrases as "status quo." Progress notes should reflect the *acute* condition of the patient.
3. Physician orders must reflect treatment of the condition for which the patient was admitted or which subsequently developed. If ancillary tests or medical therapies are ordered and are not consistent with the patient's current diagnosis or condition, they should be justified in the progress notes.
4. All abnormal test findings should be noted in the progress notes along with an assessment of the findings' impact on the patient's current condition and a plan for treatment or follow-up.
5. If antibiotics ordered do not conform with sensitivity results, the reason for the choice should be documented.
6. If a patient must undergo unplanned surgery, indications should be clearly documented.
7. Nosocomial infections, transfusion reactions or errors, medication errors, or trauma suffered in the hospital should be completely assessed by the physician in the progress notes.
8. Early efforts to arrange an adequate discharge plan for the patient should be documented.

9. A final note should reflect the medical stability of the patient on discharge. Blood pressure and temperature should be within normal limits, wounds should be clean and dry, and abnormal ancillary findings addressed with a plan for follow-up post-discharge.
10. The final summary should be a meaningful recapitulation of the patient's course of illness, hospital management, discharge plan/instructions, and a plan for follow-up care. At discharge, final diagnoses which relate to the current hospitalization should be included.

CRITERIA NORMS AND STANDARDS COMMITTEE

The Criteria Norms and Standards Committee under the co-chairmanship of Paul A. Gitman, MD, regularly meets and recommends changes for the HCFA's approval. The committee is responsible for developing all IPRO review criteria. All criteria require full approval by NCFA. The following criteria are currently under review by the committee:

1. Autologous bone marrow transplant
2. Cesarean section
3. Endocholecystectomy
4. Coronary artery bypass graft
5. Stapedectomy (change to overnight procedure)
6. Endoscopy (add criteria to approve esophagoscopy as part of evaluation of carcinoma in head/neck surgery)
7. Morbid obesity (guidelines for surgery)
8. Ophthalmology (approve criteria for Argon laser trabeculoplasty)
9. Total cholecystectomy (remove requirement for preauthorization if it is part of a more extensive procedure and not a primary procedure)
10. Psychiatry (change generic quality screen)

PHYSICIAN RELATIONS COMMITTEE

The board of directors of IPRO has established the physician relations committee in order to facilitate direct communication with organized medicine. The committee is led by Stuart Orsher, MD, a member of IPRO's board of directors and a Councilor of the Medical Society of the State of New York, and includes representatives from 11 medical societies and congressional districts. All concerns and generic problems of organized medicine will be communicated through this committee to the board.

CONCLUSIONS

IPRO's board of directors believes that all avenues should be open to all physicians, regardless of their individual affiliations, and that all members should have a voice in shaping the policy and direction of IPRO.

Shanisse

GLENN FLORES, MD

We call it The Clinic for Special Studies, but it is really the pediatric AIDS clinic. It was my second session in the clinic as a pediatric intern.

My experiences with children with AIDS up to that point had left me very impressed by two aspects: resiliency and precariousness. The resiliency defiantly jostles me whenever I meet these children and their caretakers. The children are usually self-assured, surprisingly content, and quite "normal" by subjective standards. The caretaker is usually the child's grandmother. If the parents are not already dead from drug abuse or murder, the usually unwed mother has abandoned the child or forfeited his care because of the enslavement of substance abuse. Often no one has seen the biological father for years. The grandmothers masterfully resume the parental role, seemingly nonplussed by yet another burden besides the chronic one of poverty.

The powerful undercurrent of precariousness also suffuses my impressions. Something about these otherwise "normal" children is unsettlingly colored by the imminence of AIDS. Perhaps it is the occasional glances of fear or confusion I catch in their eyes, or my own guilt at knowing that they, uninformed for their own protection, will one day have their lives shattered by pain, illness, and premature death. The otherwise admirably strong, poised grandmothers occasionally reveal glimpses of being emotionally frayed at the edges. This is understandable, after their having been yanked from the peace of retirement to become a parent again, and having to cope with the addiction or death of their sons and daughters.

When I see these patients and their families, I quickly realize that human immunodeficiency virus disease is not only immune system deficiency but a stark portrait of an all too common life of deficiency: poverty, drug abuse, deficient family, deficient health care, deficient social services, deficient education and prevention, deficient caring.

That day in the AIDS clinic it was bitterly cold outside. I looked out the windows of the clinic, hot tea cradled between my hands, and was momentarily transfixed. Frantic clusters of cars sped by on the FDR Drive. Beyond the highway the frozen East River sluggishly flowed by, choked by haphazard blocks and sheets of ice. From behind the steel, glass, and concrete of the New York City skyline a few rays of the lingering late afternoon sun poked through the open slats of the venetian blinds, dappling the table and my hands.

A nurse abruptly dropped a pile of charts on the table. I

picked up the first one, still savoring the warmth on my hands from the mug of tea. My first patient's name was Shanisse Jones. I loved the children's names I heard in this clinic—Shaquan, Latika, Idel. It was as if the creativity and uniqueness of the child's name lifted child and parent out of the monotonous cruelty and harshness of the ghetto, even if only for the moment the name was spoken. I opened the chart to check through the old records and acquaint myself with Shanisse Jones. Unfortunately, as all too frequently happens, medical records had failed to locate the old chart, and I was met with a piece of paper blank except for the name, history number, and date. Shanisse's was a story waiting to be told.

I went to greet Shanisse Jones in the waiting room. I encountered a thin, wasted-away, immobile 12-year-old child, prostrate on a row of chairs, limbs protruding through a heap of parka, lying in stark contrast to the other children frolicking and absorbed in play around her. Next to her sat her grandmother. One hand rested lovingly on her granddaughter's back, the other confidently clutched a white, 1950s-style purse. She wore a conservative navy blue dress, slightly threadbare at the hem and sleeve, with a small, tarnished silver necklace. With poise and patience she awaited the doctor, and the decaying dress and necklace worn proudly only accentuated her obvious strength and tenacity. Mrs Jones greeted me courteously and cheerfully, and nudged Shanisse, telling her to say hello to me. Shanisse noncommittally grunted in response to my hello, and unenthusiastically dragged along behind me and her grandmother as we made our way to the examination room.

I went to get the attending physician, Dr Ralston. He was a tall, robust, imposing middle-aged man with large hands and a face that at first seemed to express subtle anger. When I had first met him a few months before, I almost felt intimidated, and was surprised to learn he was a pediatrician. He won me over immediately, however, with his gentle, engaging demeanor and concern for his patients' social and family problems, as much as for physical examination findings.

Dr Ralston and I went through a routine follow-up examination of Shanisse. She lay on the crisp white paper of the examination table, enduring our questions and physical examination with a depressed, bored look and minimal verbal response. She had done fairly well since the last visit, but had continued to lose weight, and her spleen and lymph nodes were still very enlarged.

When our examination was finished we sent Shanisse to wait outside, as her grandmother wanted to talk to us alone. For my benefit, the grandmother filled me in on

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recent events.

"Shanisse is still very depressed about her mom, who died three months ago of AIDS," she said, composed and matter-of-fact. "She knows she's sick with the same thing her Mom had, but we don't tell her it's AIDS." I glanced at Dr Ralston. He listened to her with an expressionless countenance. His eyes had shifted just beyond Mrs Jones to the open venetian blinds, which revealed a bleak winter urban landscape cloaked in the last glowing light of dusk. Dr Ralston seemed to take all of what Mrs Jones had said in stride, as if he had heard such things too many times and accepted them as inevitable. Mrs Jones' statements had jolted me. I had never considered the question of whether a child should be told he has AIDS.

The clinic nurse then walked in.

"Oh, I'm glad I caught all of you together. Mrs Jones here was telling me that the visiting nurse, who was sent to help Shanisse at home, stole \$10 from her closet."

Dr Ralston and I looked at each other in shock and anger. We then looked at Mrs Jones, who simply said, "That's right," as if this were something she had been expecting to happen. Dr Ralston apologized to Mrs Jones. Then he said, "I will make sure this never happens to you and Shanisse again. Excuse us." He told me to come with him, and as he whirled around to angrily grab the door-knob, his long, white attending physician's coat slapped me in the knee, galvanizing me to follow him.

Dr Ralston called the clinic nurse over, and as we waited for her, we both leaned against the wall outside the examination room where Mrs Jones awaited us. "Can you believe that someone could do that to a kid like Shanisse?" Dr Ralston said to me. As I shook my head, I glanced over at Shanisse. She had resumed her prone, prostrate position, but now faced away from the direction of the crowded clinic playroom. The clinic nurse finished drawing blood from a screaming four-year-old boy being restrained by a teenage mother who looked bored and irritated. The nurse peeled off her latex gloves, then made her way over to us. "Betty," Dr Ralston softly said, "please find out what nursing agency Shanisse has, and let me know right away. This is the last thing our kids should have to put up with."

We returned to the examination room. "What was it you wanted to talk to us about, Mrs Jones?" Dr Ralston asked.

"What I wanted to talk to y'all about is Shanisse's father," Mrs Jones began. "He's been in jail the last couple of

weeks, but Shanisse don't know. Yesterday he died of AIDS." For the first time she revealed a slightly helpless countenance. She fingered the strap of her purse, and uncrossed and recrossed her legs. "How should I tell her? Should she go to the funeral?" She looked away, trying to regain her composure. Dr Ralston put his chin in his hand, leaned back, and let out a light sigh. I slowly looked down at the floor, studying the sharp, even cracks between the linoleum tiles. As a physician, I had rigorously trained for years to deal with crises, suffering, and disease, but now the misery simply overwhelmed me, oppressively settling on the room like a cloud of fog.

"I think Shanisse needs to know about these things, Mrs Jones," Dr Ralston began, somewhat uncomfortably, "but we can tell her in the most supportive environment possible. This means having you, me, and anyone else around who will make her feel more comfortable and cared for. She really gets along well with our social worker, Raul, doesn't she?"

She nodded in recognition and emphatic agreement, saying, "Yes, he would be great." I knew Raul well. At the end of a busy clinic day I often saw him walking slowly with a little boy on his shoulders or kneeling with a child, paint on his shirt, fingerpainting enthusiastically. We sometimes stopped briefly to talk in the hallways, cursing the Mets and then parting with our customary "high five" slap of the hands, our symbolic gesture of solidarity against the daily stresses and suffering we endured.

Dr Ralston asked Mrs Jones whether she thought it would be useful for Shanisse to go to at least part of her father's funeral. "I know she's only a child," she reflected, "but death is somethin' that everybody gots to reckon with. I had a lotta problems in my life, but I learned sometimes ya just gotta meet it all head on and beats it so ya can get on with life. We'll all be there for her when it gets rough." Nothing more need be said, I thought. She had crystallized it all perfectly. Still, though, when I see kids like Shanisse, and the victims of burns, abuse, and poverty, I can only feel sadness that we must tell young children about cruelty, pain, and death.

We all decided the meeting should happen now. Mrs Jones and I went to get Shanisse. We repeated the earlier procession, except I put my hand on Shanisse's shoulder as she moped along, parka half on, dangling from her shoulders. I led her into the room, and as I closed the door, I heard the other children joyfully playing in the waiting room.

Adenovirus infection in a neonatal intensive care unit

SHEELA G. LAUNGANI, MD; ELIZABETH ESCALANTE, MD; SHIRLEY L. KAUFFMAN, MD;
NATHAN RUDOLPH, MD; LEONARD GLASS, MD

Adenoviral infections occur in all age groups, including neonates.¹⁻³ Serious nursery epidemics are, however, unusual. In this report, initial infection occurred in a neonate who was apparently infected by his mother, although it is not clear whether the transmission was perinatal or postnatal. Within a six-week period, a fatal adenoviral infection occurred in a low birthweight infant, and two physicians assigned to the nursery had significant keratoconjunctivitis.

CASE REPORTS

Following an uneventful pregnancy, a 4-kg male infant was born by cesarean section because of fetal distress and passage of meconium. A severe aspiration pneumonia was treated with antimicrobial agents and 13 days of ventilatory assistance. When the infant was three days old, the mother, who visited daily, developed mild conjunctivitis, which was not reported to the nursing or medical staff.

Following extubation of the infant, respiratory distress persisted, with thick, yellowish nasopharyngeal secretions, persistent wheezing, and a purulent conjunctivitis. The clinical signs slowly resolved, and the infant was discharged at one month of age.

Tracheal aspirate cultures grew adenovirus; serologic typing was not performed. No pathogenic bacteria were isolated during the course of the infant's illness.

An attending neonatologist who had participated in the resuscitation of the above infant, and who had examined him daily, developed photophobia and severe keratoconjunctivitis 14 days after the infant's birth. A clinical diagnosis of adenoviral infection was made, but no viral cultures were obtained. The physician's illness persisted for two weeks.

A 1.32-kg male infant, who had not required ventilatory assistance, developed se-

vere respiratory distress accompanied by copious nasopharyngeal secretions on the fourth day of life (26 days after the birth of the reference infant, who was still a patient in the same nursery). Ventilatory assistance and antimicrobial therapy were begun; however, bacterial and viral cultures remained negative. A worsening pneumonia and seizures preceded the infant's death on the 11th day after birth.

On postmortem examination, the lungs were consolidated and abundant; thick yellow secretions filled the tracheobronchial tree. Microscopy revealed acute necrotizing bronchitis, bronchiolitis, and pneumonia, with smudgy basophilic inclusions replacing respiratory epithelium. Viral particles, 70-80 nm, in crystalline array compatible with adenovirus, were demonstrated by electron microscopy (Fig 1).

A house officer who cared for the second infant developed keratoconjunctivitis ten days after the death of this infant. A culture of the eye discharge was positive for adenovirus. Serotyping was not performed.

DISCUSSION

Adenoviral infections account for about 5-7% of respiratory illnesses in children. The virus may be shed in the stool and from the pharynx of asymptomatic carriers, and the relationship between carriage of the organism and clinical illness may not at times be clearly established.

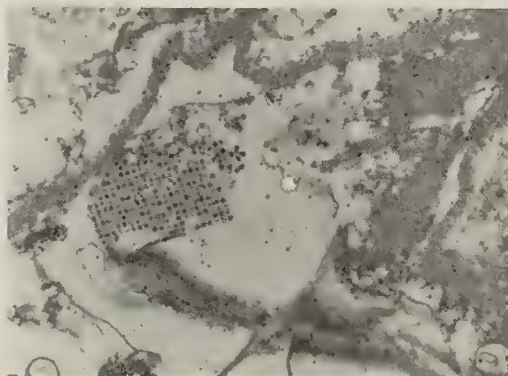


FIGURE 1. Electron microscopy showing viral particles in crystalline array, from postmortem lung sections (vinyl acetate-lead citrate stain; original magnification $\times 28,382$).

These infections are not commonly diagnosed in the neonatal period. The reasons for this are not completely understood. The presence of transplacentally acquired complement-fixing antibodies may afford protection to exposed fetuses and neonates.⁴ Failure to perform viral cultures in neonates with clinical signs of infection may be another reason.⁵

Adenoviral infection can develop during the antenatal, intrapartum, or postnatal periods.⁶ A sepsis-like clinical picture, with involvement of the respiratory tract and eye, has been reported in most instances, including these two neonatal patients,^{5,7-9} and nosocomial spread has been described.¹⁰ The mode of transmission between these two infants was most likely skin to mucous membrane contact; mother to infant in the first neonatal patient and infant to physician to infant in the second. Because of prolonged rupture of membranes in the mother of the first patient, ascending infection may be considered as a possible cause, but is unlikely. Both physicians were probably infected by self-inoculation of infants' secretions into their conjunctivae following examination of the infants. This emphasizes the importance of meticulous handwashing both before and after examining or performing a procedure on a patient.

Although adenoviral infections are usually relatively benign in older patients, they may have widespread systemic manifestations and lead to death in neonates.⁵⁻⁸ While no specific antiviral therapy is currently available for the treatment of adenoviral infections, it is nonetheless important that this group of infections be considered, for epidemiologic reasons, in the presence of significant unexplained respiratory illness in the neonate, and that viral cultures be routinely taken. The role of meticulous handwashing and careful assign-

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ment of medical and nursing personnel in the prevention of nosocomial spread of adenovirus infection cannot be over-emphasized.

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Intracranial extension of a frontoethmoidal sinus mucocele

A delayed complication of chronic sinusitis

WILLIAM F. YOUNG, MD, ROBERT H. ROSENWASSER, MD

Mucocele formation with intracranial extension is an uncommon but potentially devastating complication of longstanding sinusitis. A mucocele of the paranasal sinus is defined as an accumulation of mucus within a sinus due to blockage of the sinus ostium.¹ If left untreated, it can result in intracranial infection (abscess formation or meningitis) or, secondary to mass effect, result in damage to the orbits and contents of the anterior cranial fossa.² We describe a case of frontoethmoidal mucocele with intracranial involvement.

CASE REPORT

A 43-year-old man presented to this institution with a chief complaint of a seven-year history of right frontal headaches. He had been treated at another institution for several years for chronic sinusitis and nasal polyps. According to the patient, he had undergone 25 procedures for removal of polyps and sinus drainage. The details of these procedures are unknown.

On physical examination the patient was afebrile. There was mild tenderness over the right frontal bone. The general physical and neurologic examinations (including an eye examination) were entirely normal.

A computed tomographic (CT) scan of the head demonstrated a mass in the anterior cranial fossa (Fig 1). Additional scans demonstrated evidence of inflammatory changes in the ethmoid sinus (Fig 2). Moreover, the mass appeared to expand the posterior wall of the frontal sinus (Fig 3). A magnetic resonance imaging (MRI) scan

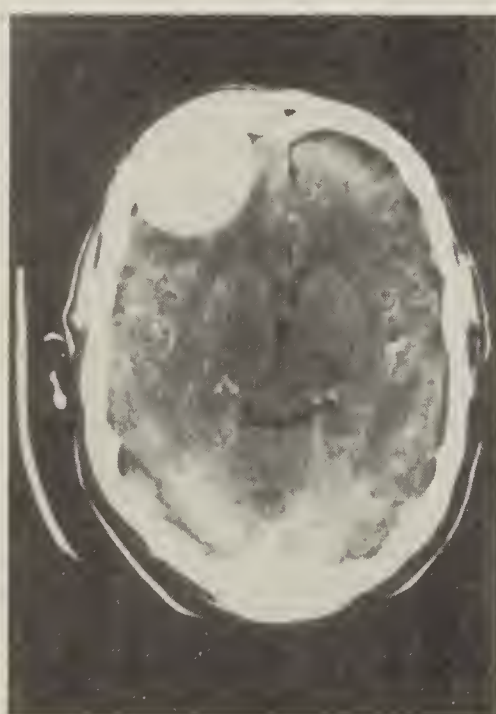


FIGURE 1. Axial contrast-enhanced CT scan of the head demonstrating highly enhanced lesion in the anterior cranial fossa.

demonstrated that the lesion was extra-axial (Fig 4).

Antibiotic therapy was begun and the patient was subsequently taken to surgery. Through a bifrontal bone flap, the mucocele was excised from the underlying dura and traced to its origin in the ethmoid sinus. There was evidence of invasion of the right orbital roof. The posterior wall of the frontal sinus was removed, followed by exenteration of the mucosa remaining on the anterior wall. The space was then obliterated with an abdominal fat graft. An osteoplastic bone flap closure was then performed. The patient then underwent bilateral Caldwell-Luc procedures with functional endoscopic surgery for removal of nasal polyps and to en-

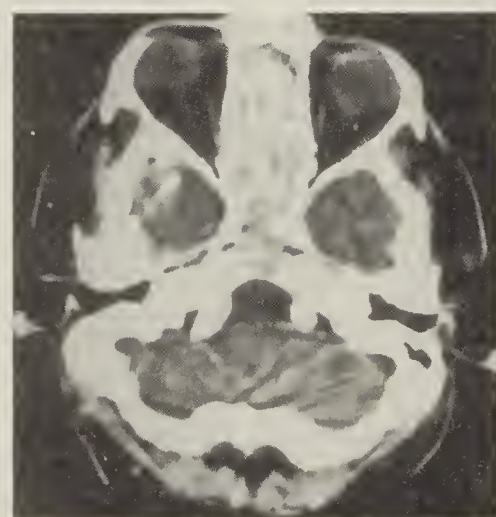


FIGURE 2. Axial CT scan of the head demonstrating chronic inflammatory changes in both ethmoid sinuses.

sure adequate sinus drainage. His postoperative course was benign, and he was discharged after a ten-day hospital stay.

At the six-month follow-up, the patient had no complaints of headache. His neurologic examination was entirely normal.



FIGURE 3. Axial unenhanced CT scan of the head demonstrating expansion of the posterior wall of the frontal sinus by a mass.

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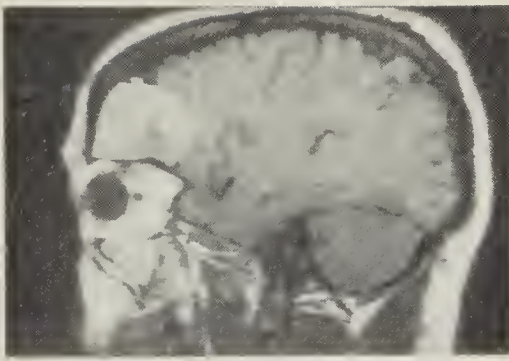


FIGURE 4. MRI (T-2 weighted) of the sagittal plane suggesting that the lesion is extra-axial.

Moreover, follow-up CT scans of the head at six months revealed no evidence of recurrence of the mucocoele.

DISCUSSION

Mucocoeles are benign lesions without sexual predilection. The term was coined by Roulet in 1896.³ However, the first reported case was by Henry Nucalai in 1785. Most patients present in the third and fourth decade of life, although there have been isolated reports of mucocoeles in children.³ Mucocoeles are cystic structures lined by low cuboidal or respiratory epithelium.⁴

There are multiple causes of the ostium blockage which results in mucocoele formation. However, sinusitis with associated inflammation occurs in 50% of

the cases.⁵ Other causes include allergy, trauma, previous surgery, anatomic variation, and, rarely, tumors (osteomas, metastases).⁶

Mucocoeles most commonly occur in the frontal sinuses (70%), followed by the ethmoid, maxillary, and sphenoid sinus. Frontoethmoidal mucocoeles commonly present with proptosis; however, this was not present in this patient.⁷ Diplopia is also a common symptom due to mass effect on orbital contents. Headache is the most common symptom. CT scanning is the most useful diagnostic modality for demonstrating sinus disease and intracranial expansion.⁸ There is usually no contrast enhancement of these lesions unless they are infected (mucopyocoele). The mass in this patient did exhibit contrast enhancement, but was found not to be grossly infected on surgery. This fact points to the variable appearance of this lesion on CT scan. MRI is also helpful since it can exclude vascular lesions from the differential diagnosis and better define relationships to intracranial contents.

Surgery is the only effective treatment for this disorder. Care must be taken to remove all vestiges of the mucocoele; otherwise it will recur. The pa-

tient in this report had undergone multiple previous procedures, and these may have contributed to the eventual formation of the mucocoele through scarring, as well as the patient's problem with longstanding sinusitis. In conclusion, invasive mucocoele is an important potential complication of chronic sinusitis with or without previous surgery and should be kept in mind when treating patients with sinus disease.

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Granulomatous peritonitis in an African man

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Granulomatous peritonitis is a disease rarely encountered at the time of surgery and often difficult to diagnose. The most frequent causes are tuberculosis¹⁻⁵ and starch from glove powder during laparotomy.^{6,7} We present a case of granulomatous peritonitis in which the diagnosis was made during exploratory laparotomy.

CASE REPORT

A 35-year-old African man, who had moved to the United States from Ethiopia one year earlier, was admitted for elective exploratory laparotomy with a preoperative

diagnosis of lymphoma. He had had persistent crampy abdominal pain for three months, associated with weight loss (10 lb). The medical history was significant for *Toxoplasma gondii* retinitis, diagnosed eight months prior to admission, for which he was treated with antibiotics and prednisone. He responded well, and the steroid treatment was stopped after five months. The patient had no history of abdominal surgery or tuberculosis. An upper gastrointestinal series and computed tomographic (CT) scan of the abdomen performed prior to admission revealed only minimal ascites and multiple enlarged retroperitoneal lymph nodes. A bone marrow biopsy was normal. The patient was referred for exploratory laparotomy and possible staging for lymphoma.

On admission, the patient was afebrile and had normal vital signs. The physical examination was remarkable for a minimally

distended abdomen, which was soft and nontender. The spleen was not palpable. There was no cervical, axillary, or inguinal adenopathy. The rectal examination was negative. Except for a mildly elevated prothrombin time of 13.8 sec, the remainder of the laboratory analysis as well as the chest film were normal.

At laparotomy, 1,000 mL of yellowish, cloudy ascitic fluid was found and was sent for analysis and cultures. The entire visceral and parietal peritoneum were found to be covered with whitish miliary nodules, 2-5 mm in size. There were some bowel adhesions, but no ileitis or colitis was noted. The retroperitoneal lymph nodes, previously reported on abdominal CT scan as suspicious, were found to be normal in appearance. Multiple biopsies of the miliary nodules were obtained. Frozen section revealed non-caseating centers with multinucleated giant cells of Langhan's type, accompanied by fi-

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broplastic proliferation and the presence of chronic inflammatory cells (Fig 1). The ascitic fluid contained 4.3/dL of protein. Based on these findings, a presumptive diagnosis of tuberculous peritonitis was considered, and the operation was terminated. Rifampin and isoniazid were started and were continued for one year.

The patient's postoperative course was uneventful. An anergy skin panel was found to be positive only for tuberculin antigen after 48 hours. Serum cryptococcal antigen as well as histoplasmosis serology were both negative. Stains and cultures for acid-fast bacilli and fungi as well as cytologic studies were also noncontributory.

At one-year follow-up, the patient had no abdominal pain or other symptoms and had gained 20 lb.

DISCUSSION

There are multiple causes of granulomatous peritonitis. A review of the literature indicates causes that can be classified as infectious,^{1,5,8} parasitic,⁹ congenital,¹⁰ and secondary to foreign bodies.^{6,7,11-17} Most commonly reported are post-intra-abdominal surgery peritonitis caused by starch in glove powder, and tuberculous peritonitis, a rare but well-recognized disease in the Western world.¹ This patient had no history of previous abdominal operations and no record of past tuberculous infection. His chest film was normal. However, a prior history of tuberculosis exposure is not always present in proven tuberculous peritonitis.²

The incidence of tuberculous peritonitis is 0.5%³ to 0.8%² of all patients with tuberculosis. The disease affects all age groups,³ mainly in the third to fourth decades.¹ The risk factors for tuberculous peritonitis are ambulatory peritoneal dialysis,⁴ alcoholism,³ and immunosuppression.⁴ Tuberculous peritonitis can also be a result of hematogenous spread from a previous pulmonary complex,^{1,3} reactivation of lymph nodes from previous lymphatic spread,¹ or direct extension from contiguous structures (ie, gastrointestinal,

or fallopian tubes).⁵ This patient had no evidence of tuberculosis elsewhere, but had in fact been treated with steroids for several months as part of the therapy for toxoplasmosis retinitis. His condition could have resulted from the reactivation of a dormant tuberculous focus, and should have prompted a preoperative skin test for tuberculous exposure.

Another infectious agent that may cause granulomatous peritonitis is *Coccidioides immitis*.⁸ Granulomatous reaction within the peritoneum has also been described in infection with *Ascaris lumbricoides*.⁹

Among the noninfectious causes of granulomatous peritonitis are ruptured dermoid cyst,¹¹ iodinated contrast materials injected during salpingograms,¹² ingested food starch from bowel perforation,¹³ postoperative contamination with cellulose,¹⁴ cotton lint¹⁵ or starch on glove powder,^{6,7} and peritoneal reaction to meconium or vernix caseosa.¹⁶ Granulomatous peritonitis has been reported in an intravenous drug abuser, and was associated with silica transmigration into the peritoneum.¹⁷

Granulomatous peritonitis usually presents insidiously with anorexia, malaise, fatigue, low-grade fever, weight loss, and abdominal discomfort.^{2,6,16,17} It almost never presents with acute abdominal pain that would indicate immediate surgery. On physical examination, abdominal tenderness and ascites are often reported.^{3,11,14,15}

Preoperative laboratory analysis contributes little to the diagnosis of granulomatous peritonitis.^{3,7,16} Delayed hypersensitivity skin testing is not always positive, and in fact has been shown to be negative in proven cases of tuberculous peritonitis.³ A positive tuberculin skin test as well as an elevated ascitic protein content are strong arguments for the diagnosis of tuberculous peritonitis, but the reverse is not true. In starch peritonitis, an intradermal starch skin test may be of value in the diagnosis.⁷

Radiographic studies are of little help in the differential diagnosis of granulomatous peritonitis.^{3,6,11,13,15} The chest radiograph may show signs of pulmonary tuberculosis,² but is often normal, as in this patient.^{1,3} Abdominal CT scan can show irregular masses and ascites.³

Tissue biopsy is the most reliable method for diagnosis of granulomatous peritonitis.^{5,6,11,13,17} In the case of tuberculous peritonitis, a caseating granuloma, even without the finding of acid-

fast bacilli, is considered diagnostic.⁵ This patient had a noncaseating granuloma, which may also be seen in tuberculosis.¹⁸

During surgery, tuberculosis⁵ and other forms of granulomatous peritonitis^{11,13,14,16} present as miliary seeding of tubercles on the serosal surface of the peritoneum; also found are intraperitoneal adhesions.^{3,6,14,17} All of these findings were noted in the patient reported on here.

In granulomatous peritonitis, therapy is dependent on the underlying causes. The disease is usually self-limiting when it is secondary to starch or cotton lint.^{6,14} Antituberculous agents are required for nine to 12 months in confirmed cases of tuberculous peritonitis.^{2,3} In suspected cases of tuberculosis, treatment is also recommended because of the favorable outcome with therapy¹ and because of the difficulty in diagnosing tuberculous peritonitis.² Corticosteroid or nonsteroidal anti-inflammatory therapy has been advocated to prevent adhesion formation from the granulomatous reaction.^{3,6,15}

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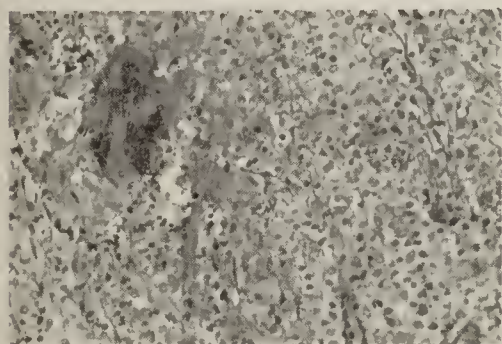


FIGURE 1. Microscopic section of peritoneal nodules showed a noncaseating granuloma (hematoxylin-eosin stain; original magnification X 200).

Persistence of detrusor hyperreflexia in a continent, institutionalized elderly patient with Parkinson's disease

PERRY STARER, MD, LESLIE S. LIBOW, MD

Urinary incontinence is a common problem in elderly nursing home patients.¹ There are a variety of pathologic processes which may present with urinary incontinence. They may be classified as follows: detrusor instability, overflow incontinence, sphincter insufficiency, functional incontinence, and iatrogenic incontinence.² Detrusor instability, which describes the presence of uninhibited detrusor contractions,² has been reported as the most common urodynamic finding in incontinent elderly patients.³ Anticholinergic medications have been utilized in the treatment of detrusor instability. Oxybutynin chloride has both an anticholinergic effect and a direct spasmolytic effect on the bladder smooth muscle.⁴

The treatment of incontinent elderly patients with detrusor instability presents a challenge to the physician. If detrusor instability were determined to be the cause of urinary incontinence in a patient, then an anticholinergic medication might be an effective treatment. However, if detrusor instability is not the sole factor related to the symptom of incontinence, then other treatment modalities would need to be considered. In order to evaluate and treat incontinent nursing home residents, a consultation service with an on-site urodynamic laboratory was established in The Jewish Home and Hospital for Aged in New York City. We present the case of an incontinent nursing home resident with detrusor instability who continued to have involuntary contractions even though he regained continence.

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CASE REPORT

A 70-year-old man with the complaints of urinary frequency, dysuria, and urge incontinence underwent evaluation two weeks following admission to The Jewish Home and Hospital. The patient was wearing protective undergarments. He had a history of Parkinson's disease, gait abnormalities, and memory loss. The patient had undergone a transurethral resection of the prostate in the past due to benign prostatic hypertrophy. He was admitted to the nursing home for rehabilitation therapy. Medications at the time of evaluation included carbidopa/levodopa, bromocriptine, and thioridazine. The patient was ambulatory, but was dependent in transfer and toileting.

On physical examination, there were no contractures, and the knee and ankle jerks were decreased, but equal bilaterally. Vibration sense, position sense, and sensation to pinprick were intact in the lower extremities and motor power was good bilaterally. A mental status examination revealed moderate dementia.

Urinalysis was negative for glucose, ketones, protein, and blood, but there were 2-3 white blood cells per high power field. Following voiding, catheterization drained a residual volume measuring 25 mL. Carbon dioxide cystometry (filling rate = 100 mL/min, 12 French catheter, supine position) demonstrated an involuntary bladder contraction at a volume of 146 mL (Fig 1). Involuntary contractions were also demonstrated when an 8 French catheter was used. There was no evidence of bladder outlet obstruction. Loss of urine with coughing was not demonstrated. The diagnosis of detrusor hyperreflexia was made, and treatment with oxybutynin (2.5 mg, three times a day) was initiated.

Seven months after the initiation of treatment, the patient was reassessed. He was continent of urine, but complained of nocturia and urinary frequency (every three hours). There had been no change in his medications (carbidopa/levodopa, bromocriptine, thioridazine) except for the addition of oxybutynin. At this time the patient was independent in ambulation and toileting and was not wearing protective clothing. There were 2-3 white blood cells per high

power field in the urine. Cystometry performed while the patient was receiving 2.5 mg three times a day of oxybutynin showed involuntary contractions at a volume of 130 mL in the supine position (Fig 1). The oxybutynin was discontinued. The patient was still continent when reassessed three weeks following the discontinuation of oxybutynin.

DISCUSSION

Detrusor hyperreflexia has been reported to be the most common urodynamic pattern in patients with Parkinson's disease.⁵ Although anticholinergic medications have been reported as useful in the treatment of patients with Parkinson's disease who have urinary incontinence,⁶ in this patient, involuntary bladder contractions persisted on cystometric examination despite the use of oxybutynin. However, the dose used may have been too low to be effective. It is interesting to note that the patient became continent despite the cystometric presence of involuntary contractions. One significant change in this patient may have been the improvement in his mobility status and his ability to toilet himself without assistance. Although he became continent, he continued to complain of urinary frequency. It appears that improvement in mobility contributed to this patient's achievement of continence in spite of the persistence of involuntary contractions. The symptoms of urinary frequency and urgency may occur in the presence of detrusor instability without being associated with urinary incontinence.⁷

There have been a limited number of clinical trials of oxybutynin in incontinent elderly patients. Neither a habit-training program alone nor one combined with oxybutynin were shown to have any significant effects on the frequency of incontinence in a placebo-controlled trial involving functionally impaired nursing home patients.⁸ In a

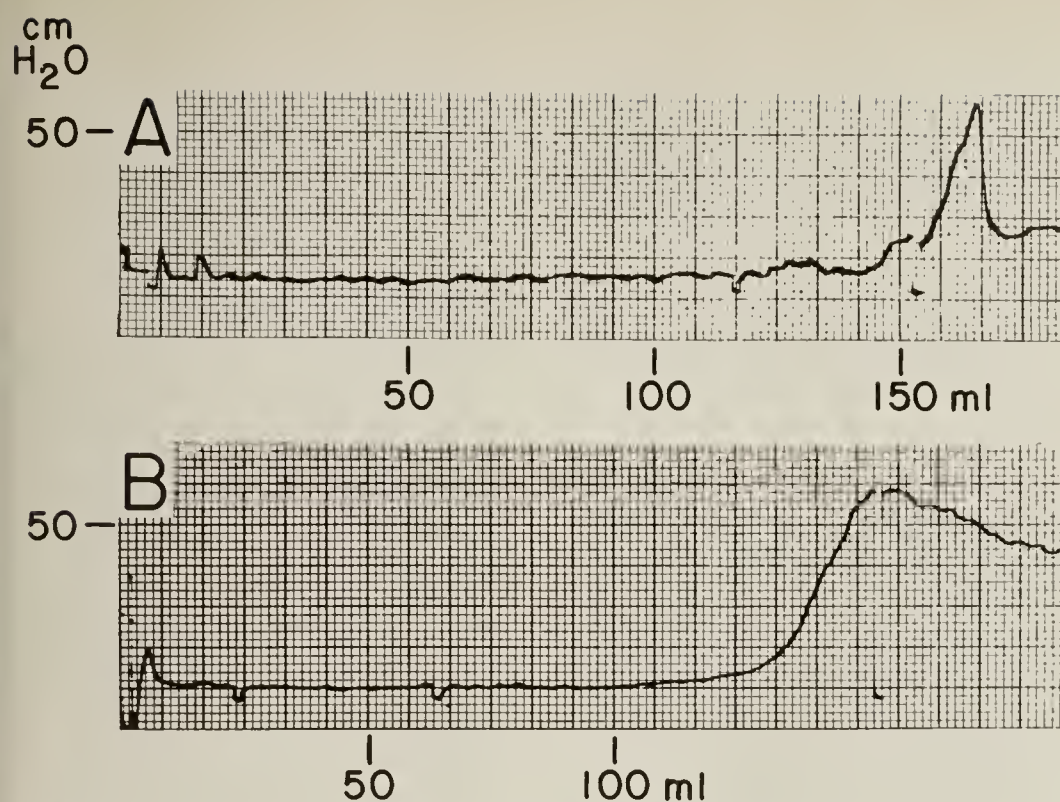


FIGURE 1. Carbon dioxide cystometry (filling rate = 100 mL/min, supine position). **A:** Involuntary contraction of the bladder at a volume of 146 mL (study terminated following contraction peak); **B:** Cystometry repeated following initiation of oxybutynin therapy. The patient was continent and involuntary contraction of the bladder occurred at a volume of 130 mL.

study of elderly institutionalized patients with detrusor instability, oxybutynin was no more effective than placebo for the treatment of incontinence.⁹ In an uncontrolled study of the effects of oxybutynin in eight adult patients with involuntary contractions of the detrusor, Diokno and Lapedes¹⁰ demonstrated symptomatic improvement in all of the patients and urodynamic improvement in seven of the eight patients. Moisey et al⁴ conducted a controlled study of 23 patients with detrusor instability (age range, 20–79 years) in which patients received 28-day courses of placebo or oxybutynin chloride (5 mg three times a day). While 17 patients (69%) had symptomatic improvement, urodynamic changes did not match the symptomatic improvement in most of them.

Urinary incontinence has been described as “the result of a predisposing factor and a precipitating factor,” in

which the predisposing factor could be detrusor instability.⁷ If the patient is able to alter his environment and lifestyle to meet the demands of an unstable bladder, he may remain continent.^{7,11} The loss of mobility or of mental clarity in addition to the presence of detrusor instability can result in urinary incontinence.¹² Detrusor instability alone in an elderly patient may not be sufficient to cause incontinence.^{13,14} However, in the setting of an additional stress such as dementia or immobility, incontinence may occur.² The use of anticholinergic medications may not alleviate incontinence in institutionalized patients unless there is also a toileting program to compensate for a patient’s limited mobility and/or cognitive dysfunction.¹⁵

In an institutionalized population, improved access to toilet facilities may be the most important treatment of urinary incontinence, whereas medica-

tions utilized to suppress involuntary contractions may be less successful than hoped. Although the findings of the patient presented here may not be representative of all incontinent patients encountered in a long term care facility, they indicate the complexity of treating urinary incontinence in this population. Further research is needed to determine the clinical significance of abnormal urodynamic findings and to assess the effectiveness of medications in incontinent elderly patients.

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The elimination of the requirement for medical libraries in hospitals

TO THE EDITOR: Dr Farnsworth's commentary on the elimination of the requirement for medical libraries in hospitals was very timely, and helps to relay to the medical community the serious impact such elimination would have on the access to and delivery of health sciences information.¹ However, Dr Wróblewski's letter to the editor on that subject instills further cause for concern.²

Although Dr Wróblewski makes some good points, he gets on the wrong track when he suggests that the availability of on-line access to information via the National Library of Medicine and other software programs will allow for decreased space requirements and decreased need for certain journals, books, etc, and result in reduced costs.² As important as this technology is in any medical library, it requires more space to house hardware, software, and necessary peripherals such as paper, telephones, communications equipment and lines. In addition, there are increased costs involved in the purchase of this equipment, and in providing training to use and service it. On-line searching incurs costs and also requires competent personnel to do an efficient job.

Unless a library is willing to do expensive full-text searching and printing, and can afford the relevant databases, or has access to the very best interlibrary lending network, it can forget about a decreased need for certain journals and texts, and of course forget cost savings. Dr Wróblewski does not support eliminating the hospital medical library. However, his assumption that on-line information access will eliminate certain space requirements and the need for conscious collection development is erroneous, in my view.

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Endometrial changes in patients receiving tamoxifen therapy

TO THE EDITOR: I would like to comment on the case report entitled "Endometrial carcinoma in five patients with breast cancer on tamoxifen therapy."¹

We previously reported on the estrogen agonistic effect of tamoxifen at the endometrial level in breast cancer patients after excluding the possible shared risk factor of hyperestrogenic state in these patients.² Because tamoxifen can act as an estrogen agonist in some circumstances we systematically follow-up our breast cancer patients on tamoxifen with a routine out-patient hysteroscopy prior to and post tamoxifen treatment.

We recently reported on our preliminary findings in 16 such patients, confirming some endometrial changes in nine out of 16 patients.³ Apart from finding proliferative changes and endometrial polyps, we also had a patient who developed an endometrium adenocarcinoma on this treatment, although no lesion had been found prior to the treatment.

We agree that endometrial screening should be part of the follow-up management for patients on tamoxifen. We could not prove a protective effect of combined progesterone treatment, but this interesting suggestion certainly must be considered in the future.

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Physician recredentialing

TO THE EDITOR: In the November 1990 issue of the *Journal*, Dr Farnsworth¹ reviewed in brief the origin of the concept of periodic physician recredentialing and then presented his conclusion that this process should be abandoned. I am pleased that Dr Farnsworth's article was published because it provides me with the opportunity to correct certain misapprehensions and also to record the growing national recognition of the need for means to improve the quality of medical care.

Dr Farnsworth focuses attention on the "clinically incompetent" physician and states that there are little or no data to support the contention that there is a significant problem of medical negligence in New York. He cites the summary statistics of the Office of Professional Medical Conduct² and the Harvard Medical Practice Study.³ It is arguable that the latter careful retrospective chart review can be dismissed as showing insignificant negligent medical care, however, inasmuch as 3.7% of the hospitalized patients reviewed experienced injuries that were the result of medical interventions unrelated to the natural history of the underlying illness. Of these injuries, 1.0% resulted from negligence that led to prolongation of hospitalization and/or disability at the time of discharge. On the basis of random sampling of the charts of 2.7 million hospitalized patients in 51 institutions, medical negligence was associated with death in 0.25% of the cases. There are at least two very important points that emerge from this only partial abstraction of the data in the massive Harvard study:

1. extrapolation of the percentages cited to the 2.7 million discharges leads to significant numbers of injuries and deaths due to medical negligence which cannot be disregarded; and
2. an examination of the reasons for the errors³ (p58) leading to adverse events identifies performance errors, prevention errors, diagnostic errors, and drug treatment errors which are not necessarily manifestations of

"incompetence" but are errors of omission and commission which could be made by any physician and are correctable.

Dr Farnsworth echoes a recommendation made by the Federation of State Medical Boards,⁴⁻⁶ namely, to identify the "bad apples" who are clearly fraudulent or impaired and also to concentrate on identifying those individuals most likely to be incompetent, particularly physicians over the age of 65 and those in solo practice without a hospital affiliation. The Ontario "Physician Enhancement Program" is cited in support of this suggestion.^{7,8} Can't you hear the cries of outrage of senior physicians, particularly some who like the author voluntarily became recertified by his specialty board more recently than many younger physicians? Or the litigation introduced by solo practitioners who would claim discrimination and violation of the antitrust laws? Quite aside from these easy state medical board solutions which would relieve the majority of physicians from public accountability, the concept is basically flawed because it does not address the fundamental purpose of periodic physician recredentialing, which is to improve the quality of average medical care as well as to identify substandard practice.

Before reviewing the current status of physician recredentialing in New York and also giving the reasons why New York doctors should welcome the process rather than trashing it, I want to review national activities which are pertinent.

For 20 or more years, there have been articles in the medical literature describing overuse, inappropriate use, and underuse of a variety of diagnostic and therapeutic measures. A seminal publication by John Wennberg⁹ in 1973 described the dramatic differences in tonsillectomy and adenoidectomy rates revealed by small area analysis which could not be ascribed to differences in the number and age of children or other factors and, by exclusion, could only be ascribed to differences in physicians' indications for carrying out the procedures. This type of analysis together with the development of appropriateness indicators for specific procedures or diseases has repeatedly documented wide differences in medical care which often reflect overuse and inappropriate use.¹⁰⁻¹⁷

Now for the shape of things to come let us look at Public Law 101-239, the

1989 amendment of the Public Health Service Act. Under the terms of this amendment, the Agency for Health Care Policy and Research (AHCPR) was created with broad responsibilities to "enhance the quality, appropriateness and effectiveness of health care services." Many of these responsibilities formerly belonged to the Center for Health Services Research, but within the AHCPR there is a Forum for Quality and Effectiveness in Health Care which involves a joint public-private effort to develop, publicize, and evaluate practice guidelines. The AHCPR has requested advice from the Institute of Medicine (IOM) of the National Academy of Sciences on how to approach the responsibilities for practice guidelines. The IOM Committee has issued its first report¹⁸ which affirms the concept that the appropriateness and effectiveness of health care can be increased by improving practice guidelines and strengthening the knowledge base for health care practice.

These are many telling comments in the IOM report which are pertinent to the subject of periodic physician recredentialing:

... the legislation establishing AHCPR is one consequence of accumulated public and private frustrations about the perceived health and economic consequences of inappropriate medical care. These frustrations and perceptions stem from many sources including ceaselessly escalating health care costs, wide variations in medical practice patterns, evidence that some health services are of little or no value, and claims that various kinds of financial, educational, and organizational incentives can reduce inappropriate utilization.^{18(p2)}

The report notes:

More generally, the creation of a practice guidelines function within AHCPR can be seen as part of a significant cultural shift, a move away from unexamined reliance on professional judgment toward more structured support and accountability for such judgment. Reflecting the first element of this shift, guidelines are intended to assist practitioners in making health care decisions; reflecting the second aspect, they are to serve as a foundation for instruments to evaluate practitioner and health system performance.^{18(pp2,3)}

These quotations make clear that action on using clinical guidelines as a mechanism for physician evaluation is a fundamental part of national planning. Surely the Health Care Financing Administration will expect its fiscal intermediaries and peer review agencies to

use the guidelines for reviewing care provided to Medicare beneficiaries.

It is to be emphasized that interest in practice guidelines has grown by leaps and bounds in recent years. The American Academy of Family Physicians took the lead, followed closely by the American College of Physicians and the American Society of Anesthesiologists. In fact, the latter organization has not only demonstrated the value of guidelines in improved outcomes but has reaped the benefit of a reduction in malpractice insurance premiums.¹⁹ Other organizations now involved in guidelines development include the Rand Corporation, the American Board of Medical Specialties, the Council of Medical Specialty Societies, and the American Medical Association. It would appear that clinical practice guidelines are not a passing fancy.

Now I wish briefly to report the status of periodic physician recredentialing in New York and attempt to present a persuasive argument for full cooperation by the medical profession. In an article on this subject which has recently been published in *JAMA*,²⁰ I have reviewed the proposed program in New York and discussed the pros and rebutted the published negative views. For physicians with hospital appointments, we have proposed peer review of physicians' records to determine compliance with guidelines or standards of practice developed by their specialty societies. A second method for recredentialing is specialty board certification or recertification. For solo practitioners or health maintenance organization (HMO) physicians there will also be peer review of patient records. We have contracted with a distinguished panel of family physicians, primary care internists, and general pediatricians to develop guidelines for the medical care of a number of clinical problems in adult and pediatric medicine which would commonly be encountered in ambulatory practice. Finally, for those physicians who are not in active practice but who wish to maintain their medical licenses, we propose the use of the SPEX examination developed by the Federation of State Medical Boards. The Advisory Committee on Periodic Physician Recredentialing emphasized that the process was to be educational, not punitive, and that if significant problems were identified in a physician by one or another of the processes described, the remedy was to be "directed educational enhancement." It was also emphasized that the methodology

would be validated by experimental trials and that all evaluations would be prospective, not retrospective.

A reasonable question to ask is whether there is any need for a formal recertification process. It should now be clear that the wide variation in medical practice patterns does indicate the importance of having reasonable standards to guide medical care. Since, however, these guidelines are either already in place or in development, why, it may be asked, is there any need to monitor compliance with these standards? The answer is that it is difficult to change behavior, not only in such personal patterns as smoking, overindulgence in food or drink, drug abuse, etc, but also in medical practice. A number of large studies have documented this problem^{21,22} with the generally accepted conclusion that guidelines, even when well known and accepted as reasonable, are unlikely to bring about rapid change in actual practice unless there are other incentives or the removal of disincentives. The incentives or disincentives which have been proposed include requirement of a recertification examination²³ or stopping reimbursement.²⁴ The recertification process proposed in New York is not so draconian and, in fact, is "physician friendly."

As the reports on recertification in New York have emphasized, the methodology of peer review is being validated. The trials have been going forward in obstetrics and psychiatry and it is expected that peer review trials in otolaryngology, anesthesiology, emergency medicine, and ambulatory medicine will be carried out within the current year. The reviews are confidential; the hospitals, physicians, and reviewers are all protected legally against any liability; the procedures are designed to be educational; and the physicians in these trials have the opportunity to comment on the validity of the guidelines that have been developed by their national specialty organization. The peer reviewers are chosen for their recognized clinical qualifications and their objectivity is unquestioned.

It is to be noted that these and other incentives do have an effect on medical practice. The classical example was the follow-up on Wennberg's⁹ study of small area evaluation of tonsillectomy and adenoidectomy. When, after publication of the data, there was no change in the rates, representatives of the Vermont State Medical Society made site visits to a number of hospitals. There

was a rapid decline in the tonsillectomy and adenoidectomy rates and the guideline indications for the procedures are now generally accepted.²⁵ In New York the publication of the cesarean section rates showing wide variation between regions and even hospitals within the same area led to the creation of a state task force with representatives of the American College of Obstetricians and Gynecologists which developed defined indications for surgical birth. These were disseminated to all obstetrical services. Nonpunitive, confidential peer review was then initiated in hospitals throughout the state, large and small, teaching and non-teaching, municipal and private, with both high and low cesarean section rates. The results after one year demonstrated that the cesarean rates declined dramatically in the hospitals with high rates and there was even a small but statistically significant decrease in the state rate for the first time in 20 years.²⁶

If we in the medical profession accept, perhaps grudgingly, that we have an obligation, as in other essential services, to demonstrate that our practice conforms to reasonable standards, then the peer review mechanism is more appropriate, more educational, and more effective than either a written examination or review by nonmedical personnel who will have to go "by the book." Now is the time to participate in these preliminary trials so the process can be improved before formal action is taken.

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In reply. Dr Gellhorn's letter to the editor regarding my commentary¹ was predictable in both length and content. I do not think this is the forum for duplicating the former in response to the latter. However, I will make a few brief observations.

Since Dr Gellhorn did not take exception to the summary statistics of the Office of Professional Medical Conduct (OPMC) supporting my contention, I assume he concurs. I agree the Harvard Medical Practice Study is "arguable," but I argue that it, too, supports my contention that there are little or no data to support significant clinical negligence in New York State.

Dr Gellhorn clearly does not understand the recommendation to use the Federation of State Medical Board's mechanism for evaluation of *all* physicians for reregistration, and he confuses

the Peer Assessment Program with the Physician Enhancement Program.

The complex issue of the development and application of practice parameters is evolving. The linkage between practice parameters and "recredentialing" is not clear and I would indeed be skeptical of any "physician friendly" mechanisms.

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1. Farnsworth PB: A reevaluation of physician recredentialing. *NY State J Med* 1990; 90:531-532.

Cross-dressing successfully treated with fluoxetine

TO THE EDITOR: Virginia Jorgensen, MD, is too modest in crediting fluoxetine for her rapid and successful treatment of a 60-year-old married cross-dresser.¹ Her psychotherapeutic and marriage-healing skills were far more important, in my opinion, and any of a number of drugs would probably have produced the same good result.

On the first day of treatment, Dr Jorgensen's skillful handling and acceptance, assisted by a drug which calmed the patient, let him feel relaxed, and able to sleep merely by putting on a woman's nightgown. His impulse to cross-dress rapidly disappeared, he reestablished a positive relationship with his wife, and then started a new career.

I believe that Dr Jorgensen's effective psychotherapy, beginning at the very first visit, was far more responsible for this therapeutic triumph than the medication she used.

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1. Jorgensen VT: Cross-dressing successfully treated with fluoxetine [letter]. *NY State J Med* 1990; 90:566-567.

TO THE EDITOR: In the case described by Jorgensen¹ in the November 1990 issue of the *Journal*, the "patient responded with astonishing speed" and showed signs of improvement "by the evening of the first day." It is more likely that the initial improvement was due to the nonpharmacological part of the intervention. According to the case report, the patient's symptoms became more apparent after his retirement and after his wife "moved out of the bedroom." His self-esteem was most likely seriously challenged and traumatized by those events. During the course of therapy his wife participated in the process and "was able to reestablish a positive relationship with her husband." Later on, the patient was able to find another employment opportunity as well.

It appears that the therapeutic intervention, consisting of counseling for the patient, his wife, and use of fluoxetine, was helpful in lessening and/or alleviating the symptoms. I wonder whether the administration of fluoxetine was the

most significant factor in this case.

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1. Jorgensen VT: Cross-dressing successfully treated with fluoxetine [letter]. *NY State J Med* 1990; 90:566-567.

In reply. In Dr Lehrman and Dr Shabry's responses to my report of a case of cross-dressing treated with fluoxetine, they point out that more credit should be given to the psychotherapeutic intervention and the lessening of stress in the patient's life than to the medication used. To this I can respond that the patient (husband) proved to be a very unwilling subject for psychotherapy and the couple remained emotionally estranged until the target symptom was removed, with the husband no longer engaging in cross-dressing. He then assured his wife he no longer even felt the urge to do so. I was then able to work with his wife's remaining anger.

Obviously, as in most cases, psychotherapy was part of the total management, but the sense of well-being experienced by this patient within three or four weeks was so dramatic that a physiological response to fluoxetine does seem to have played an important role.

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HODGKIN'S DISEASE: THE CONSEQUENCES OF SURVIVAL

By Mortimer J. Lacher, MD, and John R. Redman, MD. 447 pp, illustrated. Philadelphia, Lea & Febiger, 1990. \$80.00 (hardcover)

With the advent of intensive radiation therapy and chemotherapy, physicians are now able to follow Hodgkin's disease patients who have survived for long periods. However, a price has been paid for this success, with long term complications, many of which result in early death.

In their book, *Hodgkin's Disease: The Consequences of Survival*, editors Lacher and Redman set out to analyze the long term effects of therapy on Hodgkin's survivors. Because of the complexity of the subject, they have taken the view that it is reasonable to blame almost everything that happens to the survivors on the effects of treatment itself.

It is very helpful to clinicians treating patients with Hodgkin's disease to have a textbook available that details the complications of therapy. This volume is a multi-authored text that encompasses all aspects of the topic. The initial chapters are devoted to general overviews and in the second half of the book the effects on individual organ systems are detailed. The necessary background is given to permit an understanding of the pathogenesis of the long term effects of therapy. The chapter by Loeffler et al on the late effects of radiotherapy provides the reader with a review of the physical and technical aspects of radiation therapy and then discusses the effects of radiation on each organ system. Similarly, Dr Kempin provides an overview of normal hematopoiesis prior to detailing the pathogenesis and occurrence of myelodysplasia and leukemia.

The occurrence of second primary cancers in patients treated for Hodgkin's disease is well documented. Acute leukemia was the first of such malignancies to be recognized, but as patients are followed for longer periods of time, non-Hodgkin's lymphoma and solid tumors are being seen. Shottenfeld reviews the epidemiology of the second malignancies in the first chapter of the text. In subsequent chapters the late effects of radiation therapy and chemotherapeutic agents are covered.

The immunodeficiency state associated with Hodgkin's disease is well documented, as are the effects of treatment and staging procedures, specifically splenectomy. Immunologic and infectious aspects are also covered in detail in three distinct chapters.

In addition to covering the clinical aspects of treatment effects, the text also addresses psychosocial consequences and legal issues. In the final chapters, the editors analyze the consequences of survival and attempt to provide guidelines for future therapy to maintain the level of success and minimize the long term complications of treatment.

In general, the text's authors present their subject with clarity and accuracy, and each chapter can stand alone as reference material. One weakness of the text is that certain chapters appear not to be sufficiently up to date. The chapter on immunocompetence provides an excellent review of immunology but lacks recent references. This is unfortunate for a field that is rapidly changing.

This book is the first text specifically focused on this subject. The concepts of therapy are addressed in other texts, but without the detail provided here. It will be a welcome addition to the library of physicians treating patients with Hodgkin's disease. It achieves the authors' stated objectives of detailing the consequences of survival in Hodgkin's disease. It also serves as a reminder to all of us of the effects of successful therapy of Hodgkin's disease and of the need to identify less toxic but still effective therapies.

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ANTIVIRAL AGENTS AND VIRAL DISEASES OF MAN

Third Edition. By George J. Galasso, PhD, Richard J. Whitley, MD, and Thomas C. Merigan, MD. 800 pp, illustrated. NY, Raven Press, 1990. \$150.00 (hardcover)

This is the third edition of a well-known, multi-authored textbook on the use of antiviral agents in the treatment of human disease. The book is directed at a very wide audience, from pharmacologists to clinicians, from medical students to experts. This edition has two

editors from the previous editions who are both leaders in the development of antivirals, and a third, new editor whose expertise in the clinical testing of antivirals brings still further strength to the team. In addition, many of the contributors are highly respected leaders in the fields of clinical virology and antiviral agents.

The book covers nearly all aspects of viral therapeutics, from good chapters on the development and testing of candidate compounds, to reviews of many of the most important clinical viral diseases and the use of specific agents in their management. The material is generally presented clearly and accurately, although some chapters are quite wordy and could have benefited from better editing. As with many multi-author volumes, the depth of coverage of the various topics varies tremendously. I would have preferred a fuller discussion of the issues of pre-clinical toxicologic assessment of these drugs, or of the problems of using some of these agents in certain special risk groups, including pregnant women, children, and the elderly. However, in general the coverage is good and gaps can usually be supplemented with the standard virologic and infectious disease texts.

Another problem common to multi-author texts is overlap among chapters. Because the editors have chosen to approach the material both by organ system and by pathologic agent, there are some problems with repetition of some topics, and fragmentation of others. Herpes simplex virus, for example, is discussed in four different chapters, and even the more specific topic of neonatal herpes simplex infection is covered in some detail in two different places. Similar problems arise with certain other viruses which can involve several different systems, such as the enteroviruses or cytomegalovirus. The arrangement works better for those viruses which are closely associated with only a single organ system, or a single dominant clinical syndrome, for example, the hepatitis A virus. Topics are also repeated in somewhat different form in more than one chapter, for example, the cellular bases of viral infection and replication, which are covered both in chapter 1 on the targets of antiviral agents, and in chapter 2 on the pathogenesis of viral infection. A few of the chapters, such as the one

on ocular infections, substantially overlap with other chapters, and might not offer enough additional material to warrant separate chapters in future editions.

Because the field of clinical virology is so rapidly changing, no book can be entirely up to date. This book already needs some updating on such topics as status of acyclovir for the treatment of varicella-zoster infections, the fetal chickenpox syndrome, or perinatal human immunodeficiency virus infection. For several chapters, few of the bibliographic citations are more recent than 1986. For the next edition, the editors might consider a brief addendum chapter at the end of the volume for additional references that become available while the book is in press. However, the book does have excellent coverage of such topics as the use of ribavirin in some of the exotic viral hemorrhagic fever syndromes, and the role of interferon in the treatment of chronic hepatitis B infection. The greatest strength of this book is its excellent discussions of the pharmacology, experimental therapeutics, and, in many cases, the clinical value of the growing spectrum of antiviral agents now, or soon to be, available to the clinician. These would include acyclovir, ganciclovir, azidothymidine, and a variety of compounds currently under investigation. Antivirals are now an established part of regular clinical practice, both in the hospital and in the office, and for education in this important area, this volume is a good place to start.

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THE OCULAR FUNDUS: A PHOTOGRAPHIC DOCUMENTATION ATLAS WITH DIAGNOSTIC AND THERAPEUTIC GUIDELINES

By Horst Huismans, MD. English translation by Manfred R. Tetz, MD, and David J. Apple, MD. 215 pp, illustrated. Baltimore, Williams & Wilkins, 1990. \$129.50 (hardcover)

Horst Huismans' *The Ocular Fundus* was originally published in German in 1986. As an atlas, it offers uniformly high quality photography of the retina, comprising over 300 color plates. These illustrations should prove to be an excellent reference source for medical students, residents, and practitioners,

as intended per Dr Huismans' preface. Details of the posterior pole of the normal retina, its variants, congenital anomalies, and hypertension-related changes are especially well documented. The photographs are all from the author's practice in affiliation with the Munster University Eye Clinic in Munich.

The format of the book is very attractive, with a well-organized text preceding the accompanying color plates of each chapter. Brief reviews of normal anatomy, physiology, and examination techniques are followed by summaries of most of the important retinal, choroidal, and optic nerve diseases. A caption presenting the case history accompanies nearly every fundus photograph.

The text of this German atlas may be interesting to American ophthalmologists for its occasional differences in approach to various diseases in terms of classification, pathophysiology, and treatment. For example, Dr Huismans offers up isovolemic hemodilution as an intervention for branch retinal vein occlusion, involving lowering the patient's hematocrit to 30%, an unlikely management option for the ophthalmologist in this country. The exceedingly rare diagnosis of "spontaneously regressed retinoblastoma" might provoke argument among ophthalmic pathologists here and abroad. Some foreign eponyms and colorful descriptive terms appear, such as the "inverted Napoleon's hat," referring to the appearance of preretinal hemorrhage.

The Ocular Fundus is not always up to date. Its having been published originally in 1986 prior to its English translation has perhaps resulted in some limitations. For instance, the ocular manifestations of human immunodeficiency virus infection are not covered; the section on cytomegalovirus retinitis makes no mention of acquired immunodeficiency syndrome or ganciclovir. There is a striking absence of discussion of the treatment of diabetic retinopathy, ie, panretinal laser photocoagulation for proliferative disease and focal laser treatment for selected cases of diabetic maculopathy, which treatments have been studied extensively and are the standard of care in the United States. Laser treatment is mentioned in conjunction with retinal vein occlusions, but the rationale for its use is not made clear. Similarly neglected are the roles of cryotherapy for retinopathy of prematurity and of vitrectomy for various forms of retinal detachment and other vitreoretinal disease.

As a whole, *The Ocular Fundus* is a well-produced, beautifully illustrated photographic atlas. Its text is most often worthwhile and provides some interesting and controversial cross-Atlantic twists in ophthalmic language and approach. It may be faulted for its dated and uneven attention to the therapy of a variety of important and treatable retinopathies.

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DOWN SYNDROME: THE FACTS

By Mark Selikowitz, MD. 205 pp, illustrated. North Carolina, Oxford University Press, 1990. \$18.95 (hardcover)

This book was written as a guide to parents raising a child with Down syndrome. As the director of Tumbatin Developmental Clinic at the Prince of Wales Children's Hospital in Sydney, Australia, Dr Selikowitz is well qualified to write the book, which seeks to guide parents from the time of discovery of their child's condition towards the goal of maximizing his adult potential and independence.

The book attempts to cover a vast amount in its 200 pages, including the stresses of discovering that a child has Down syndrome and coping with explaining the news to others. Also included is an explanation of the syndrome itself and how it comes about, the development of physical milestones and skills, health problems associated with Down syndrome, behavioral problems, and training, schooling, and intervention programs and services available to help the child and his or her family. The particular problems of adolescence and adulthood, an anecdotal section on controversial treatments for Down syndrome, and prenatal diagnosis options available to detect Down syndrome in future pregnancies complete the coverage.

In attempting to cover this much material, some areas are, understandably, better explained than others. Some of the early chapters on parental and family response to the new child are somewhat choppy and superficial, while others, such as the lengthy sections on development and assessment, are fairly detailed.

I found the section on the health of Down syndrome children particularly strong. Dr Selikowitz first describes the

basic health maintenance required for these children, and then focuses on specific conditions which they encounter more frequently than their "normal" peers. Descriptions of thyroid dysfunction, duodenal atresia, and orthopedic problems, among others, are basic and clear. A separate chapter is devoted to specific cardiac problems. The language here is somewhat more complex, but should still give the average parent a good idea of what these conditions entail. The only point I dispute here is Dr Selikowitz's schedule of routine health checks, in which a physical examination is recommended at birth and at age six weeks, then annually thereafter. While it is suggested that children follow a "routine immunization schedule," the time course is not specified, and new parents need to know that complete physicals are important at several points during the first year of life for *all* children.

In general, an effort is made to make the language basic and understandable. However, American readers will note the different phrases used by the Australian author, such as "nappy" for diaper, and teaching the child to "pass a motion" when describing toilet training.

Overall, I found *Down Syndrome: The Facts* to be a realistic guidebook for parents. The author is optimistic about each child's potential and encourages parents to find joy in their child's individual accomplishments. At the same time, he continually reiterates the reality of Down syndrome, that there is no cure, that new parents may feel guilty, angry, or embarrassed for their child, and that respite care, allowing time away from the demands of their child, may be a positive option for both the youngster and his or her family.

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WORK WITHOUT STRESS: A PRACTICAL GUIDE TO EMOTIONAL AND PHYSICAL WELL-BEING ON THE JOB

By Samuel H. Klarreich, PhD. 176 pp. New York, Brunner/Mazel Publishers, 1990. \$17.95 (clothcover)

Samuel Klarreich has written a highly readable book that can help people understand and change their own patterns in the workplace. In clear language geared to the lay reader, he guides one through the steps of identi-

fying the warning signals of stress, its impact on the body, and the all too common spiral from the drive to succeed to overdrive and agitation, with the accompanying emotional, occupational, and physical risks.

The basic organizing premise of the book is that how one perceives stressful events is the key to the deadly spiral in which Type A's feel trapped. By the same logic, if one can interrupt one's behavior long enough to identify the beliefs that are disabling (such as, "I must be in control at all times," or "my worth as a person is exactly equated to my job performance") a person can then make the choice to arrive at new ideas and beliefs that can free him or her to respond with new, less stressful behaviors. The author underscores the importance on both an individual and corporate scale of valuing the reflective and introspective process as much as, if not more than, the action process, and sprinkles in anecdotes from his practice to bring the message home.

The second part of the book deals with burnout. It includes discussion of the warning signals, symptoms, beliefs, and the highly emphasized "counter-think" strategy that can help readers change their own beliefs in order to reduce burnout and improve job performance. The author is very clear in his delineation of the worried, anxious, and agitated person who is likely to experience the kind of stress that leads to cardiac or other health problems as distinguished from the more pessimistic, depressed person who is more likely to develop the apathy, resignation, and isolation typical of burnout.

Klarreich credits Albert Ellis as a major influence in his work, and indeed he recommends a step by step, highly rational approach that will surely be congruent for many readers. The one concern I would raise about the book is that in his enthusiasm for the effectiveness of a highly rational approach, perhaps not enough support is offered to those readers who need to accept their feelings about their problems before they can accept a strategy for change. It is certainly possible that finding the most useful mix of empathy and retraining techniques is a highly personal, stylistic distinction which is at times largely influenced by gender.

In addition to being a useful book for physicians to recommend to their patients, the book also raises questions that professionals in the medical community may wish to consider for themselves. Certainly, the culture of the

health care industry in this country has a compelling way of pulling the concerned professional toward the serious risks of stress and burnout. This may provide an opportunity for us all to pause and take stock of the way we are approaching our careers and our lives.

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PRACTICAL MEDICAL HALACHAH

Third Revised Edition. By Fred Rosner, MD, and Harav Moshe Tendler, PhD. 191 pp. Hoboken, NJ, KTAV Publishing House, Inc, 1990. \$18.95 (hardcover)

This book is a guide on how to practice 1990s medicine and still live in accordance with the precepts of Jewish law. This is indeed a formidable task for the clinician as well as for the authors of this fine work. Rabbi Tendler and Dr Rosner are well known in the Jewish community and in the world of secular medical ethics as experts in this area. This third edition has been greatly expanded and revised and covers the numerous advances that have been made in the medical field which generate complex and difficult questions of Jewish law. The volume is divided into general sections including "The Sabbath," "Mental Health," "Death and Dying," "Dentistry," and others. Within each section are listed the questions that pertain to that subject and the question/answer/explanatory comment format follows that of the earlier editions. As before, the style is clear, concise, and very readable. All sections have been expanded with new practical questions. Besides appending a reprint of the authors' article on "Physiologic Decapitation" published in the *Journal of Contemporary Halachah*, another special feature is the addition of a listing of medical responses of Rabbi Moses Feinstein. Though previous editions of this book have spawned other works of a similar nature, it remains the classic in the field and the "gold standard" to which others are compared. This book is clearly directed at health care professionals, though the subject matters discussed will be of great interest to Jewish scholars and laymen alike. It is a must on the shelf of all practicing Jewish clinicians concerned with these issues.

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Video Review

AIDS IN YOUR LIFE

By Medical Video Productions. 1 Videotape, 20 minutes. \$49.00. Rental \$35/2 weeks. Featuring James W. Curran, MD, Director, AIDS Program, Centers for Disease Control, and Robert H. Taylor, MD, Past President, American Academy of Family Physicians.

AIDS CARRIERS IN MY PRACTICE

By Medical Video Productions. 1 Videotape, 28 minutes. \$89.00. Rental \$45/2 weeks. Featuring James W. Curran, MD, AIDS Program, Centers for Disease Control, Paul M. Feorino, PhD, Chief, AIDS Virology Laboratory, Centers for Disease Control, and Robert H. Taylor, MD, President of the American Academy of Family Physicians.

As the human immunodeficiency virus (HIV) epidemic expands, the burden of caring for HIV-infected patients is gradually shifting from specialists to primary care providers. In growing numbers, people are coming to their personal physicians with concerns about possible HIV risk factors and are requesting HIV antibody testing. In high prevalence areas and, increasingly, elsewhere, primary care physicians are an important resource for management of HIV infection, at least in its early stages.

Despite the growing medical armamentarium for treatment of HIV disease, the most potent weapon against the continued growth of the epidemic remains education. The general population needs to learn the nature of HIV disease, the ways in which it is transmitted, the precautions which must be taken to protect oneself from infection, and the remedies available to those who harbor the virus. Primary care physicians need to learn to recognize and manage HIV disease and to counsel and educate their patients about it. To date, the educational efforts in both these areas have been inadequate. These two videotapes, produced by the same com-

pany and sharing much of the same content, are new resources for HIV education directed to these two important audiences, *AIDS in Your Life* to the general population, and *AIDS Carriers in My Practice* to primary care physicians.

Through a combination of direct narration, commentary by nationally recognized authorities in the field, and staged encounters between experienced clinicians and actors representing patients, both tapes systematically review the major risk factors for HIV infection and the role of the HIV antibody test. *AIDS in Your Life* provides guidance on risk reduction and conveys a strong message that by behaving responsibly, individuals can protect themselves and others. *AIDS Carriers in My Practice* instructs primary care providers on the elements of HIV screening and counseling. Both tapes cover the essential information adequately and may be used to introduce these topics to the uninitiated or reinforce basic ideas for those who already have some knowledge of these areas.

Unfortunately, both tapes are marred by serious technical errors and by reinforcement of unfortunate and hurtful stereotypes. On the most basic level, the tapes constantly blur the important distinction between HIV infection and full-blown AIDS, using misleading terminology like "AIDS test" and "AIDS carriers" rather than the more accurate "HIV test" and "HIV carriers."

Much more seriously, both tapes repeatedly state that "there is no treatment" for the HIV-positive patient, suggesting that seropositives can only be counseled to maintain healthy life styles and avoid infecting others. Nowhere in either tape is there mention of zidovudine (AZT) or *Pneumocystis carinii* pneumonia (PCP) prophylaxis, the mainstays of treatment which have been shown to prolong life and maintain health in many HIV-positive patients.

Some of the counseling interactions portrayed are less than exemplary. On both tapes, a physician counsels a newly married couple about their HIV risks, asking each about their premarital sexual activities in a single joint interview.

The husband's admission of prior contact with prostitutes elicits a look of embarrassed astonishment from his wife. The narrator on one tape admits that this counseling is best done individually, while the incident is allowed to pass without comment on the other tape.

Similarly, a physician's exploration of a male patient's sexuality begins with the question, "You're married, aren't you?"—a phrasing likely to put many gay people on the defensive and make some less likely to volunteer an accurate sexual history. The patient replies that he is single, and the physician follows up with, "Have you ever had any homosexual experiences in the past?," still avoiding the possibility that the patient might be an active homosexual. Fortunately, the actor-patient in this encounter reveals himself as gay with remarkable equanimity. The tapes would have done much better to model a more accepting, open-ended interview style, beginning perhaps with, "Do you have sex with men or women or both?" Such questions, while initially less comfortable for some physicians and patients, are far more likely to lead to accurate identification of patients at risk.

The tapes both use white models for interview scenes focusing on homosexuality and blood transfusions, but when the subject changes to drug use, the models suddenly become African-American or Hispanic. This not only perpetuates the negative stereotype of racial minorities as drug abusers, but it suggests that white patients need not be questioned about drugs and minority patients need not be questioned about homosexuality. Obviously, every patient needs a thorough history of both sexual and drug-use risk factors, regardless of his or her racial or ethnic origin.

These videotapes contain much useful information and address a real need for clear and accurate educational material on the HIV epidemic. It is to be hoped that future videos on these topics will do so with greater precision and sensitivity.

BRUCE SOLOWAY, MD
Institute for Urban Family Health
Bronx-Lebanon Family Practice Center
Bronx, NY 10456

BOOKS RECEIVED

AIDS

AIDS Clinical Review 1990. Edited by Paul Volberding and Mark A. Jacobson. 280 pp, illustrated. New York, Marcel Dekker, Inc, 1990. \$89.75 (hardcover)

AIDS and Other Sexually Transmitted Diseases: Adolescent Medicine. Edited by Manuel Schydlower, MD, Mary-Ann Shafer, MD. 647 pp, illustrated. Philadelphia, Hanley & Belfus, Inc, 1990. \$28.00 (hardcover)

CARDIOLOGY

Cardiac Catheterization, Angiography and Intervention. Fourth Edition. Edited by William Grossman, MD, and Donald S. Baim, MD. 698 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$59.50 (hardcover)

ENDOCRINOLOGY

The Thyroid Gland. Edited by Monte A. Greer, MD. 608 pp, illustrated. New York, Raven Press, 1990. \$95.00 (hardcover)

HEALTH SERVICES

The Medical Triangle: Physicians, Politicians, and the Public. By Eli Ginzberg. 314 pp. Cambridge, Mass, Harvard University Press, 1990. \$27.50 (hardcover)

HISTORY OF MEDICINE

Aztec, Medicine, Health and Nutrition. By Bernard Ortiz de Montellano. 308 pp, illustrated. New Brunswick, NJ, Rutgers University Press, 1990. \$40.00 (cloth), \$15.00 (paper).

History of Pediatrics 1850-1950. Edited by Buford L. Nichols, MD, Angel Ballabriga, MD, Norman Kretchmer, MD. 315 pp, illustrated. New York, Raven Press, 1991. \$56.00 (hardcover)

INFECTIOUS DISEASE

Viral Infections of Humans: Epidemiology and Control. Edited by Alfred S. Evans, MD. 829 pp, illustrated. New York, Plenum Publishing Corporation, 1989. \$75.00 (hardcover)

Infection Control: Dilemmas and Practical Solutions. Edited by Kenneth R. Cundy, Bruce Kleger, Eileen Hinks, and Linda A. Miller. 212 pp, illustrated. New York, Plenum Press, 1990. \$59.50 (clothcover)

INTERNAL MEDICINE

Critical Care Medicine: The Essentials. By

John J. Marini, MD, and Arthur P. Wheeler, MD. 326 pp, illustrated. Baltimore, Md, Williams and Wilkins, 1989. \$27.00 (softcover)

Managing Asthma. By Miles Weinberger, MD. 330 pp, illustrated. Baltimore, Md, Williams & Wilkins, 1990. \$37.95 (softcover)

Principles of Ambulatory Medicine. Third Edition. Edited by L. Randol Barker, MD, John R. Burton, MD, Philip D. Zieve, MD. 1,487 pp, illustrated. Baltimore, Md, Williams & Wilkins, 1991. \$99.00 (clothcover)

MISCELLANEOUS

The Purification Prescription. By Sheldon Saul Hendler, MD, PhD. 300 pp. New York, William Morrow & Co, 1991. \$22.95 (clothcover)

The Complete Guide to Women's Health. Revised 2nd Edition. By Bruce D. Shepard, MD, Carroll A. Shephard, RN. 502 pp, illustrated. New York, Plume, 1990. \$15.95 (softcover)

Walk It Off! 20 Minutes a Day to Health and Fitness. By Suzanne Levine, DPM. 257 pp. New York, Plume, 1990, \$8.95 (paperback)

Research Proposals: A Guide to Success. By Thomas E. Ogden, MD, PhD. 413 pp, illustrated. New York, Raven Press, 1991. \$39.00 (softcover)

Continuing Care: The Management of Chronic Disease. Second Edition. Edited by John Hasler, OBE, and Theo Schofield, MA. 349 pp, illustrated. New York, Oxford University Press, 1990. \$42.50 (clothcover)

Textbook of Performing Arts Medicine. Edited by Robert Thayer Sataloff, MD, Alice G. Brandfonbrener, MD, Richard J. Lederman, MD. 448 pp, illustrated. New York, Raven Press, 1991. \$88.00 (hardcover)

Social Work in Health Care: A Handbook for Practice. Part I and Part II. Edited by Kay W. Davidson, DSW, and Sylvia S. Clarke, MSC. Part I, 517 pp, illustrated, Part II, 935 pp, illustrated. Binghamton, NY, The Haworth Press, 1990. \$89.95 (set only) (hardcover), \$49.95 (softcover)

Zachary's New Home: A Story for Foster and Adopted Children. By Gerald M. Blomquist, MSW, and Paul B. Blomquist. 32 pp, illustrated. New York, Brunner/Mazel Publishers, 1990. \$5.95 (paperback), \$16.95 (clothbound)

Skin Game. By Michael Brodin, MD. 383 pp. New York, Kensington Publishing Corp, 1990. \$4.50 (paperback)

Cocaine in the Brain. Edited by Nora D. Volkow, MD, and Alan C. Swann, MD. 250 pp, illustrated. New Brunswick, NJ, Rutgers University Press, 1990. \$40.00 (clothcover)

NEUROLOGY

Parkinson's Disease: A Guide for Patient and Family. Third Edition. By Roger C. Duvoisin, MD. 219 pp, illustrated. New York, Raven Press, 1991. \$15.95 (paperback), \$30.00 (hardcover)

OBSTETRICS-GYNECOLOGY

Vaginal Surgery. Third Edition. By David H. Nichols, MD, Clyde L. Randall, MD. 463 pp, illustrated. Baltimore, Md, Williams and Wilkins, 1989. \$76.00 (hardcover)

ONCOLOGY

Neuroblastoma: Tumor Biology and Therapy. Edited by Carl Pochedly, MD. 409 pp, illustrated. Boca Raton, Florida, CRC Press, Inc, 1990. \$99.50 (hardcover)

ORTHOPEDIC SURGERY

Arthroscopy of the Knee: Diagnosis and Treatment. By W. Norman Scott, MD. 252 pp, illustrated. Philadelphia, W.B. Saunders, 1990. \$95.00 (hardcover)

PEDIATRICS

Assessing Pediatric Practice: A Critical Study. By Raymond S. Duff, MD, edited by Charles D. Cook, MD. 237 pp. Ann Arbor, Michigan, Health Administration Press, 1990, \$27.00 (hardcover)

PATHOLOGY

Color Atlas of Clinical Oral Pathology. By Brad W. Neville, DDS, Douglas D. Damm, DDS, Dean K. White, DDS, Charles A. Waldron, DDS. 381 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$89.50 (hardcover)

PSYCHIATRY

Hypochondria — Woeful Imagining. By Susan Baur. 250 pp. Berkeley, Calif. University of California Press, 1988. \$9.95 (paperback), \$25.00 (clothcover)

Psychotherapy with College Students. Group for the Advancement of Psychiatry. Formulated by the Committee on the College Student. Report No. 130, 160 pp. New York, Brunner/Mazel Publishers, 1990. \$15.95 (paperback), \$21.95 (hardcover)

Scary Night Visitors: A Story for Children with Bedtime Fears. By Irene Wineman Marcus and Paul Marcus, PhD. 32 pp, illustrated. New York, Brunner/Mazel Publishers, 1990. \$5.95 (paperback), \$16.95 (hardcover)

Couples Group Psychotherapy: A Clinical Practice Model. By Judith Coche, PhD, and Erich Coche, PhD. 192 pp. New York, Brunner/Mazel Publishers. 1990. \$25.00 (hardcover)

PUBLIC HEALTH

Under the Safety Net. The Health and Social Welfare of the Homeless in the United States. Edited by Philip W. Brickner, MD, Linda Keen Scharer, MUP, Barbara A. Conanan, RN, Marianne Savarese, RN, Brian C. Scanlan, MD. 439 pp, illustrated. New York, WW Norton & Co, 1990. \$27.95 (clothcover)

The Sanitarians: A History of American Public Health. By John Duffy. 330 pp. Champaign, Ill, University of Illinois Press, 1990. \$32.50 (clothcover)

RADIOLOGY

MRI of the Musculoskeletal System. Second Edition. Edited by Thomas H. Berquist, MD. 559 pp, illustrated. New York, Raven Press, 1990. \$130.00 (hardcover)

SPORTS MEDICINE

Winter Sports Medicine. By Murray Joseph Casey, MD, Carl Foster, MEd, Edward G. Hixson, MD. 425 pp, illustrated. Philadelphia, F.A. Davis Co Publishers, 1990. \$65.00 (hardcover)

SURGERY

A Practical Guide for Experimental Microvascular Surgery. By Kenneth E. Korber, PA,

Jeanne G. Halpern, BS. 311 pp, illustrated. St Louis, Mo, Warren H. Green, Inc, 1990. \$47.50 (softcover)

Vascular Surgical Techniques: An Atlas. Second Edition. Edited by Roger M. Greenhalgh, MA. 433 pp, illustrated. Philadelphia, W.B. Saunders, 1989. \$165.00 (hardcover)

Techniques in Arterial Surgery. Edited by John J. Bergan, MD, and James S.T. Yao, MD. 447 pp, illustrated. Philadelphia, W.B. Saunders, 1990. \$110.00 (hardcover)

TOXICOLOGY

Carbon Monoxide Poisoning. By K.K. Jain, MD. 220 pp, illustrated. St Louis, Mo, Warren H. Green, Inc, 1990. \$37.50 (softcover)

Heart valve patients urged to notify implant registry

Medic Alert Foundation (Turlock, Calif) has initiated a program to locate and register all persons in the United States and Canada who have an implanted Bjork-Shiley Convexo-Concave (C-C) heart valve. Although there has been no increased risk of failure of the implanted heart valve, Medic Alert hopes to register all people with C-C heart valves with the confidential International Implant Registry (IIR) in order to provide them with any future information about the heart valve, its risk of failure, and what to do in case of heart valve failure.

The effort to identify the estimated 23,000 people with C-C valves will involve a review of medical records by more than 450 hospitals in the United States and Canada, contacts with cardiologists and cardiac surgeons, communications in medical journals, and the availability of a toll-free telephone number (1-800-245-1492) to call Medic Alert.

Each year there are an average of seven incidents of strut failure per 10,000 C-C valves; strut fracture, in which one of the valve's struts breaks, is a life-threatening situation that requires surgery to replace the valve. Inclusion in the IIR assures a person of receiving any information concerning the safety of the C-C heart valve. The IIR encompasses people with any type of implant, including pacemakers or artificial joints.

Two drugs that target Alzheimer's disease come under scrutiny

The Food and Drug Administration (FDA) recently released an interim report questioning the accuracy in reporting of a study that described "encouraging initial results" with the drug tetrahydroaminoacridine (tacrine or THA) in treating patients with moderate to severe Alzheimer's disease (*N Engl J Med* 1991; 324:349-352). The report by Summers et al appeared in 1986 in the *New England Journal of Medicine* (1986; 315:1241-1245). Reports such as this prompted Warner-Lambert Co. to evaluate THA as a treatment for Alzheimer's disease.

The FDA contends that there are important discrepancies between the presentation of the study in the published article and the actual methodology, shedding doubt on the validity of the results. Based on its investigation of the clinical findings, the FDA questioned the randomness with which patients were assigned to a treatment group, and the assertion by the authors that all of the data were collected under blinded conditions. The FDA concluded that, "At best, we consider the evidence to be the equivalent of uncontrolled, anecdotal clinical information." Furthermore, FDA investigators found it odd that Summers and colleagues presented no "laboratory evidence of hepa-

tocellular injury" in their paper, given the findings "in subsequent clinical studies, in which approximately 20 percent of those exposed to doses of tacrine half as large as those used by Dr. Summers had clinically important aminotransferase elevations."

In response, Summers et al have stated that the FDA's allegations have no basis, and that the FDA report "is more in the nature of a personal attack on our group than of a scientific critique."

In another controversy, Hydergine (Sandoz Ltd, Basel, Switzerland) is currently the only drug on the market approved for treating persons with Alzheimer's disease. This drug recently came under attack by Public Citizen, a non-profit consumer group, which petitioned the FDA to revoke its approval of Hydergine (*Wall Street Journal*, February 13, 1991, p B4).

Public Citizen based its petition on a published study that found Hydergine to be ineffective in slowing the progression of Alzheimer's disease. A spokesman for Sandoz cited 54 studies that support the effectiveness of Hydergine and downplayed the attention focused on the study that disputes the drug's effectiveness. However, that study contained evidence that Hydergine may have a negative effect on cognitive function in some patients with Alzheimer's disease.

The FDA responded to the petition by stating its intention to review the evidence that led to Hydergine's approval status.

Immediate diagnosis of herpes simplex encephalitis achieved

Using the polymerase chain reaction (PCR) technique to amplify virus-specific DNA, Aurelius et al were able to detect herpes simplex encephalitis on hospital admission in 41 of 43 patients (*Lancet* 1991; 337:189-192). In the future, this method could eliminate the need for a brain biopsy to isolate the virus itself or to demonstrate viral antigen.

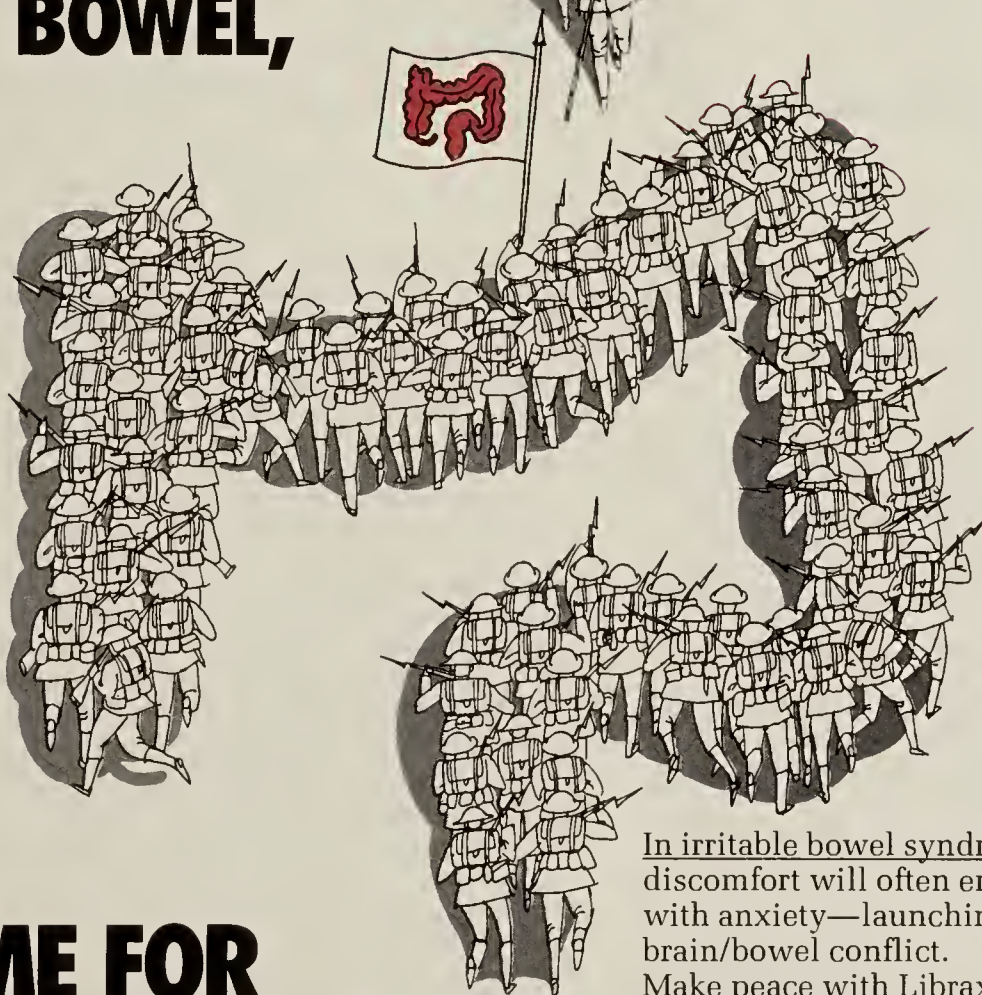
In this controlled study, the authors tested 151 samples of cerebrospinal fluid (CSF) from 43 patients with biopsy or necropsy verified herpes simplex encephalitis and 87 CSF samples from 60 control patients with acute febrile focal encephalopathy. PCR was positive for herpes simplex virus DNA in 41 of 43 patients with viral encephalitis and in no control patients. This method proved sensitive for herpes simplex virus DNA for at least five days after the initiation of antiviral therapy with acyclovir. Incorporating a weak positive control sample and analyzing duplicate samples makes the PCR technique a highly reproducible diagnostic tool, despite the complexity of the test procedure.



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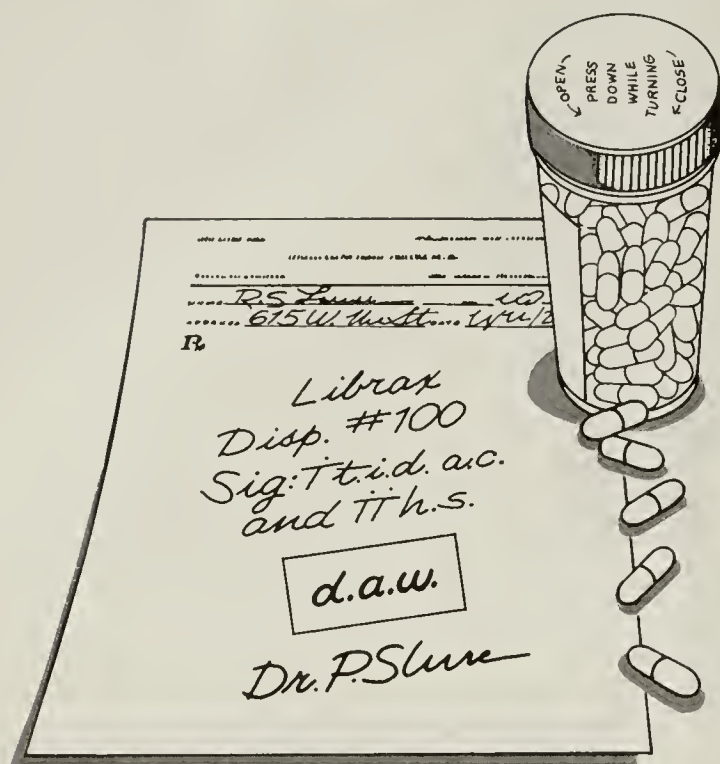
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Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur. Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such

as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Revised: February 1988

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MISCELLANEOUS

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MISCELLANEOUS—CONT'D

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(continued from p 3A)

Contact: Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear and Throat Hospital, 210 E 64th St, New York, NY 10021. Tel: (212) 838-9200, ext 2776.

May 4. Pharmacologic Stress Tests. 3½ Cat I Credits. **May 18. Assisted Reproductive Technologies: Present and Future Directions.** **May 23-24. Computers and Nursing Practice.** NYU Medical Center. Contact: NYU Medical Center, Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

May 5. Third Annual Symposium on Treatment of Headaches and Facial Pain. Halloran House. Contact: Alexander Mauskop, MD, Director, The Downstate Headache Center, 132 Atlantic Ave, Brooklyn Heights, NY 11201. Tel: (718) 935-9666.

May 16-18. Fifth Annual International Vascular Symposium. 22 Cat I Credits. Marriott Marquis. Contact: Ann J. Boehme, CMP, Associate Director for

Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042. Tel: (718) 470-8650.

AROUND THE NATION

CALIFORNIA

May 16-18. 24th Annual Advances and Controversies in Clinical Pediatrics. 16 Cat I Credits. Fairmont Hotel, San Francisco. Contact: Extended Programs in Medical Education, Room C-124, University of California School of Medicine, San Francisco, CA 94143. Tel: (415) 476-4251.

May 23-25. Contrast Enhanced Magnetic Resonance. Silverado Country Club and Resort, Napa Valley. Contact: Society of Magnetic Resonance in Medicine, 1918 University Ave, Suite 3C, Berkeley, CA 94704. Tel: (415) 841-1899.

ILLINOIS

May 18. Communication Approaches

for Tracheostomized and Ventilator Dependent Patients. Chicago. Contact: Voicing, 2857 Birch, Suite 194, Newport Beach, CA 92660. Tel: (714) 856-2419.

MARYLAND

May 15-17. Biological Effects and Safety Aspects of Nuclear Magnetic Resonance Imaging and Spectroscopy. Hyatt Regency, Bethesda. Contact: Marketing Dept, New York Academy of Sciences, 2 E 63rd St, New York, NY 10021. Tel: (212) 838-0230.

MISSOURI

May 1-3. Protection for Research Risk. Hyatt Regency. St Louis. **May 17-18. Low Back & Sciatic Pain.** Washington State University Medical Center. St Louis. Contact: Cathy Caruso, Office of Continuing Medical Education, Washington University School of Medicine, 660 S Euclid, Box 8063, St Louis, MO 63110. Tel: (800) 325-9862.

PENNSYLVANIA

May 6-8. Neurotoxins and Their Potential Role in Neurodegeneration. Adams Mark Hotel, Philadelphia. Contact: Marketing Dept, New York Academy of Sciences, 2 E 63rd St, New York, NY 10021. Tel: (212) 838-0230.

SOUTH CAROLINA

May 23-25. Annual Spoleto Update in Family Medicine. Omni Hotel, Charleston. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077. Tel: (404) 552-9859.

VIRGINIA

May 20-22. Oxytocin in Maternal, Sexual and Social Behaviors. Crystal Gateway Marriott, Arlington. Contact: Marketing Dept, New York Academy of Sciences, 2 E 63rd St, New York, NY 10021. Tel: (212) 838-0230.

WASHINGTON

May 19-22. 14th Annual National Conference on Rural Health. Westin Hotel, Seattle. Contact: Robert Quick, Communications Director, National Rural Health Association, 301 E Armour Blvd, Suite 420, Kansas City, MO 64111. Tel: (816) 756-3140.

AROUND THE WORLD

CANADA

May 1-5. American Back Society, Spring Symposium on Back Pain. 18½ Cat 1 Credits. Royal York Hotel, Toronto, Ontario. Contact: Aubrey A. Swartz, MD, Executive Director, American Back Society, 2647 E 14th St, Suite 401, Oakland, CA 94601. Tel: (415) 536-9929.

May 13-17. Thoracic Imaging 1991. 30 Cat 1 Credits. Four Seasons Yorkville Hotel, Toronto. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077. Tel: (404) 641-9773.

FRANCE

May 25-June 1. Fifth Annual Paris in the Spring, Meeting for Cardio-Thoracic and Vascular Anesthesiologists. Paris. Contact: G. Silvay, MD, Dept of Anesthesiology, Mount Sinai School of Medicine, 1 Gustave L. Levy Pl, Box 1010, New York, NY 10029. Tel: (212) 241-7630. □

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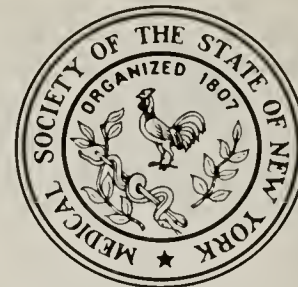
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VOL 91
NO 5
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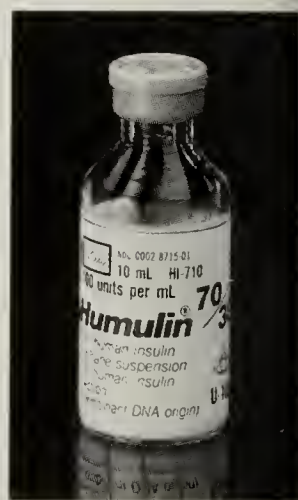
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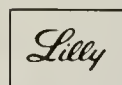
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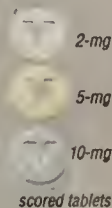
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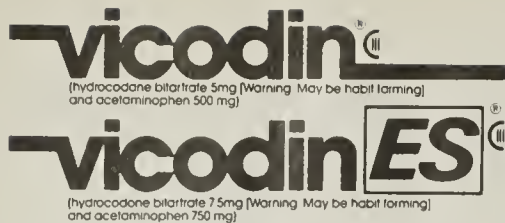
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Special Risk Patients: VICODIN/VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

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Labor and Delivery: Administration of VICODIN/VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN/VICODIN ES Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence and mood changes.

Gastrointestinal System: The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN/VICODIN ES Tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

DRUG ABUSE AND DEPENDENCE:

VICODIN/VICODIN ES Tablets are subject to the Federal Controlled Substance Act (Schedule III). Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN/VICODIN ES Tablets should be prescribed and administered with caution.

OVERDOSAGE:

Acetaminophen Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Hydrocodone Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

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June 4, June 15. Child Abuse and Maltreatment Identification and Reporting. Bellevue Hospital Center. Contact: Susan Callaghan Montella, RN, Emergency Care Institute, Bellevue Hospital Center, 3rd Floor, Administration Bldg, New York, NY 10016. Tel: (212) 561-6561.

June 7. Fourth Annual Paul Henkin Day—Ophthalmology Symposium. 6½ Cat I Credits. New York Helmsley Hotel. Contact: Albert Einstein College of Medicine/Montefiore Medical Center, Office of Continuing Education, 3301 Bainbridge Ave, Bronx, NY 10467. Tel: (212) 920-6674.

June 7. The How To's in Physical Medicine: Treatment Options in Low Back Pain. Beth Israel Medical Center. Contact: Beverley R. Baptiste, Medical Education Office, Beth Israel Medical Center, First Ave at 16th St, New York, NY 10003. Tel: (212) 420-2849.

June 10-14. 11th Annual Emergency Medicine Seminar. 25½ Cat I Credits.
June 17-20. 14th Annual Review: Selected Topics in Pediatrics. 21¾ Cat I Credits. NYU Medical Center. Contact: NYU Medical Center, Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

NEW HYDE PARK

June 12-14. The Surgical Treatment of Anorectal Malformations. 21 Cat I Credits. Schneider Children's Hospital of Long Island Jewish Medical Center. Contact: Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Cen-

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June 7. Evaluation of Abnormal Pap Smears. Southampton Hospital. Contact: Susan O'Rourke, CME Coordinator, Medical Staff Office, Southampton Hospital, 240 Meeting House Lane Southampton, NY 11968.

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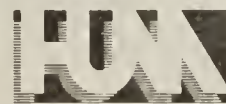
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COMMENTARIES

Nephrology in the inner city

In the inner city, the minority is the majority, poverty is usual, and crime, alcoholism, and narcotics addiction are highly prevalent. The American inner city is not a walled urban ghetto with sharply defined geographic limits. In New York City, the inner city is a series of neighborhoods with unemployment as high as 60%, fatherless households for as many as 75%, and death in young adults most often due to murder or the acquired immunodeficiency syndrome (AIDS). The Council on Ethical and Judicial Affairs of the American Medical Association has recently chronicled the "persistent, and sometimes substantial, differences . . . in both need and access" to health care experienced by American blacks who live largely in inner city ghettos.¹ Blacks are less likely than whites to receive kidney transplants, open heart surgery, and first class obstetrical or internal medicine care.² As concluded by this Council: "Whether the disparities in treatment decisions are caused by differences in income and education, socio-cultural factors, or failures by the medical profession, they are unjustifiable and must be eliminated."¹ Several serious kidney disorders—nephrosis due to progressive focal sclerosis,³ heroin-associated nephropathy,⁴ and human immunodeficiency virus associated nephropathy⁵—have a higher attack rate in blacks than in whites. Burnett⁶ suggests that a genetic defect may be responsible for the increased susceptibility of blacks to renal injury.⁶ A genetic predisposition to diabetes mellitus unquestionably contributes to the four times greater rate of renal failure due to diabetes noted in blacks when compared to whites.⁷

The practice of medicine in the inner city forces compromises. Babies born into homes without books or role models of success lose interest in education. Exposure to the school of the streets means early contact with crack, alcoholism, prostitution, and gang violence. Blunted expectations limit chances for escape into the rest of the country. Preventive medicine in the inner city, though recognized as important, becomes secondary to crisis intervention practiced in overcrowded emergency rooms. Delay in admission forces waits as long as five days for a hospital bed, even for the acutely ill.

Nephrology in the inner city, at least in Brooklyn, has evolved into the practice of socioeconomic medicine. Most renal consultations generated at Kings County Hospital in Brooklyn, NY, are for problems directly related to poverty and race. Diabetic nephropathy, hypertensive nephropathy, heroin associated nephropathy, alcohol induced acute and chronic renal failure, and AIDS associated nephropathy consume the time of the renal consultant. Blacks in the inner city face an attack rate for renal failure which is four times that of whites. Black and Hispanic uremic patients are less likely to receive a kidney transplant than are whites. Hypertension, kidney disease, and other stresses of the ghetto translate into a higher rate of psychiatric morbidity and health problems in blacks when compared with whites.⁸ Once renal failure develops, blacks are less likely than whites to adhere to a dietary regimen prescribed during maintenance hemodialysis⁹ or to the drug regimen established for renal transplant recipients.¹⁰ Surprisingly, and as yet unexplained, blacks have higher survival than whites when treated for renal failure by maintenance hemodialysis or peritoneal dialysis.¹¹

Given these dimensions of differences in incidence, prevalence, and severity of renal disease in inner city blacks and Hispanics when compared with whites, it seemed worthwhile to assemble a group of experts to explore the nature and impact of kidney disease in residents of the ghetto. Accordingly, on September 18, 1990, a symposium was held at the State University of New York, Health Science Center at Brooklyn, to examine the special aspects of renal disease and its treatment in the inner city of New York. A study of the papers generated by this symposium, some of which are published in this issue of the *Journal*, will generate despair over our current inability to alter the inexorable course of pediatric AIDS associated nephropathy, balanced by growing optimism resulting from the success in retarding the loss of renal function in diabetic nephropathy. How much of the excess burden of renal disease borne by inner city residents is actually related to genetic predisposition, as opposed to the consequences of being poor, remains to be determined. What is

evident from the papers and discussions generated by the conference, however, is the inverse relationship between overall socioeconomic position in life and the risk of contracting disorders likely to induce renal failure. Renal disorders and responses to illness by poverty burdened ghetto residents may be less the consequence of racial predilection to glomerular damage than the result of malnutrition, exposure to habituating and addicting drugs, and other as yet unquantified aspects of being disadvantaged.

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The health of poor and minority people in the inner city

It is well known that the most important determinants of health or illness are the economic, social, and physical environments in which people live rather than the quality of their medical care or even the quality of their conventionally defined health care. Surrogate measures for standard of living (such as gross national product (GNP) per capita or distribution of income) or for its specific components (such as the percentage of women who are able to read) have been shown to be critical determining elements in mortality rates (as measured by age-specific rates such as infant mortality rates or summary rates such as life expectancy at birth) and in morbidity rates, particularly for illnesses known to be preventable by measures such as immunization, safe water, adequate food supplies, good education, and protection from environmental hazards.

Care for the individual who has become ill is of course important, but its importance almost always lies in the improvement of quality of life for people who are ill or their families and rarely in the reduction of mortality rates for the population. I do not mean to suggest that medical care is not an important element in making people's lives better, through reduction in anxiety and amelioration of symptoms or of other sequelae of illness. Good medical care for people with renal disease, for example, can be extremely important in the quality of their lives and can even result in life extension for some patients. A number of the papers in this issue of the *Journal* devoted to Nephrology in the Inner City describe the continuing struggle to provide adequate medical care in the face of extraordinary barriers.

But the task of medical care is generally limited to attempts to "bind up the wounds." The wounds have usually

been made long before the patient arrives for medical care and often continue to be made, despite good medical care, in the homes (or lack of them), in the work (or lack of it), and in the communities in which people live.

For this reason, many physicians throughout the history of medicine have accepted as a part of their work attempts to maintain the health of their patients, often referred to these days as "preventive medicine" in contrast to "public health" or "social medicine." There is no doubt that such efforts, the precedents for which extend back to Hippocrates, can help to maintain or even improve the health of many individuals and families. The problem with this approach, however, is its focus on "patients" (people cared for by a doctor or other elements of the medical care system) rather than on everyone in the community, and, perhaps even more important, its focus on the patient's individual life style choices. Nonetheless such interventions can be useful. If physicians and other health workers were better trained in providing them and better motivated to spend their time on them, their patients would be better served.

But for most patients, and unquestionably for most people in the community, such techniques barely scratch the surface in dealing with the determinants of poor health. Most of these determinants largely lie outside the control of individuals or of families. Nutrition and other elements of nurturing during the prenatal period; adequate diet and living conditions during infancy and childhood; good education; resistance to community pressures to use tobacco, alcohol, and other drugs; safety in the home, workplace and streets; and protection from environmental hazards are of major importance in determining not only the quality of life but morbidity and mortality levels as well. Counselling individual patients and families on these issues, important as that counsel may at times be, often constitutes "blaming the victim" rather than accomplishing signifi-

Based on a presentation at the "Symposium on Inner City Nephrology," sponsored by the Nephrology Foundation of Brooklyn and the Renal Disease Division, Department of Medicine, State University of New York Health Science Center at Brooklyn, NY, September 18, 1990.

cant change in these determinants.

The specific ways in which people in the inner city are victimized are well known. Many of these conditions exist in urban areas beyond the inner city, and in rural areas as well, but our focus here is on the inner city. The US census and surveys in individual cities demonstrate the inadequacy of housing and the large numbers of people who have no permanent housing at all. Surveys of increasing sophistication demonstrate a high prevalence of hunger and malnutrition in city after city. Inner city populations are surrounded by pressures to use harmful substances and these pressures (advertisements for cigarettes are a good example) are often focused on minority populations. Hazards in the workplace and in the environment are important factors; levels of lead and asthma-causing pollutants, for example, are often highest in areas where poor and minority people are concentrated. Racism continues to deny equal opportunity and to increase the risks to those seen as different by the dominant group.

The overarching victimization is, of course, poverty, which has been increasing over the past decade. The United States now has the greatest gap between rich and poor in the history of the gathering of these statistics. One-fourth of all children under the age of five in the United States live below the officially designated "poverty line" and one half of all African-American children under the age of five live below that level. Furthermore, the poverty line is purposely set low to hide the magnitude of the problem and millions of children and adults who are forced to live at levels 50% or 100% above the line may also be in terrible need.¹

The health consequences of these living conditions are also well known. These include more low birthweight babies; higher neonatal, post-neonatal, and childhood mortality rates; infectious diseases that might have been prevented by immunization; learning and behavioral disorders associated with hunger, homelessness, and elevations in blood lead levels; asthma and other breathing disorders associated with air pollution; injury and death from intended and unintended violence; and of course many of the nephrologic problems being discussed here today.

What is to be done? Dealing effectively with these inner city problems is virtually impossible for doctors and other health workers, however well-informed and well-motivated they are, if they act alone. It is only through political action, by health workers acting together and in conjunction with others, that there is any hope of meeting these urgent needs.

In the long run we will need a fundamental restructuring of a society in which many live in poverty so that a few can live in obscene luxury. But in the short run much can be done. Those efforts usually lie more in the realm of the community, in "public health" or "social medicine," rather than in the individual realm of "preventive medicine." Some societal responses are relatively easy, such as restricting advertising of cigarettes and their easy availability which help entrap young people into the addiction of smoking. Much harder are the development of programs for nutrition, housing, education, and public safety.

There are ways to develop such programs in inner city medical settings. For example, our department has

worked with people who live in the apartment buildings that surround Montefiore Medical Center in a 16-week series of seminars and demonstrations, one evening a week, about three hours each evening. Our neighbors learn technical skills like cardiopulmonary resuscitation and how to take blood pressures. Even more important, we think, they learn health education methods for work with their neighbors; they learn how to teach neighbors how to use the health care system more effectively, how to use preventive services, and how to organize the neighborhood for safety and for health.

The neighborhoods around Montefiore and in many parts of the Bronx are changing rapidly. For many groups our course was taught in Spanish because that was the language in which our volunteers will work with their neighbors. At the end of the 16 weeks, a graduation is held to congratulate people, to present them with a diploma and a badge, to honor them for the work they have done, and to encourage them to keep using their skills in the neighborhood. About three weeks after one of these ceremonies, one of the graduates died in a terrible accident. She was riding her bicycle in the Bronx and was killed by a truck speeding by. The other people in the program ran to help with the three young children she left. We would have anticipated that. When the family laid her out for her burial, they did so in the dress that she had worn to the graduation ceremony. That need not have surprised us; it was probably her best dress and would be used for the wake and the burial. What did surprise us was that the family had pinned to her dress, for the wake and the burial, the badge she was awarded at graduation proclaiming her a member of the program. That badge was for us a means of identification so graduates could be recognized by personnel in our clinics and emergency room if they came in with patients; for the graduate, it had other significance. The family told us she had never before experienced a graduation ceremony and because she was so proud of having learned skills with which to help her neighbors, they thought she would like to go to her grave wearing the symbol of these skills.

Each of these groups as they go through the program develops a slogan. This group's slogan was:

Para lograr grandes cosas
No solo debemos actuar
Si no también soñar,
No solo planear
Si no también creer.
To accomplish great things
We must not only act
But also dream,
Not only plan
But also believe.

This program was supported at its inception in the 1970s by a grant from the White House. In 1981, in the middle of a grant year, the new Reagan Administration cancelled the grant. That was part of a broader withdrawal of funds from health and other services. For example, from 1982 to 1986, there was a 82% fall in federal funds for housing, a 52% fall in federal funds for employment and training, a 28% fall in funds for mass transit, and a

20% fall in funds for community development (all corrected for inflation); on the other hand the military received a 38% increase after inflation.²

Where are the resources for such programs to come from? Some funds could, of course, be transferred from military spending, the so-called "peace dividend," but the amounts likely to be made available for the purposes we are discussing, even if military spending is cut, will not meet our needs. But there is another source. At this point approximately 35% of our national wealth is owned by the top 1% of our population, very similar to the situation in 1929, which was followed by the economic correction called the "Great Depression." There was then a fall, to 23% of wealth owned by the top 1%.³ Now, as a result of the breaks for the rich and other economic advantages for them, we're back to an obscene and dangerous maldistribution of wealth. Higher taxes on the wealthy and on corporations is the only just response to the maldistribution, and also happens to be an answer to our need for publicly financed services.

Sweden, which may collect too much in taxes, collects them at a level of 57% of its gross domestic product (GDP) at the national, provincial, and local level. Sweden is followed, in descending order of percent of GDP collected, by Denmark (51%), the Netherlands (46%), Norway (46%), Belgium (45%), France (44%), Luxembourg (43%), Austria (41%), Ireland (39%), Italy (38%), Finland (38%), West Germany (38%), Great Britain (37%), Greece (36%), Portugal (35%), Spain (34%), Canada (33%), Switzerland (32%), Iceland (32%), Japan (31%), Australia (31%), and the United States, which collects only 30% of the GDP in taxes.⁴ To meet the needs of our people, the United States will have to move from its current tax levels to the levels of Western Europe, from 30% to 35% or even 40% of GDP, with the burden falling appropriately on the rich through steeply progressive taxation rates.

Is advocacy of increased tax revenues and of the program for which they are needed indeed part of the professional work of the physician and other health workers? Rudolph Virchow, a Berlin pathologist who developed the cellular theory of pathology and among many other contributions discovered the significance of and invented the terms "thrombus" and "embolus," was asked by the Prussian Government in 1948 to investigate a raging epidemic

in Upper Silesia. The causes of the medical problems, he reported, were government neglect and oppression, poverty, religious exploitation, and illiteracy. His recommendation included education in the Polish language, self-government, separation of church and state, shifting of taxes from the poor to the rich, improvement of agriculture, development of cooperatives, and the building of roads. Virchow taught that it was as much a part of the physician's role to work for social change in the name of health as to deal with the treatment of individual patients.^{5,6}

I am aware that physicians and other health professionals who provide care to inner city patients with kidney disease are already desperately overburdened. But unless they, together with others outside the health care system, devote some of their extraordinary skills and their time and energy to the prevention of the social, economic, and environmental causes of their patients' conditions, their current patients will continue to be harmed and endless numbers of new patients will arrive to seek their help. For their own professional well-being, as well as to meet urgent needs of their communities and their patients, health professionals in the inner city will have to add to their already heavy burdens an additional task: efforts to improve the living conditions and to lessen the environmental risks for their patients and for others in the communities they serve.

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Imaging techniques and asymptomatic renal cell carcinomas

The data presented by Sigalow et al¹ in this issue of the *Journal* confirm the observation that the classically described triad of symptoms of renal tumor—hematuria, pain, and mass—no longer are acceptable criteria for making the diagnosis. As a result of improved diagnostic techniques, these are late signs and symptoms of ominous prognostic significance. The increasing utilization of pyelography, computed tomography, and, in particular, ultrasonography have resulted in the increasing incidental

recognition of asymptomatic renal tumors. Unfortunately, still to be proven by long term studies is improved survival as the result of the early recognition of the renal tumors. Along with the improvement in diagnostic techniques has come the recognition of varying pathologic characteristics of cortical renal tumors which apparently also alter prognosis. Renal tumors of the papillary pattern seem to have a better prognosis clinically than nonpapillary tumors and the oncocytic type of proximal tubular

renal carcinomas are for all practical purposes benign in their behavior.

Unfortunately modern imaging techniques do not permit preoperative identification of such differences which apparently influence the prognosis, as does earlier detection and surgical techniques. Hopefully, in the coming years, as a result of molecular biologic studies and newer and more advanced diagnostic, pathologic, and immunologic techniques, a further understanding of the biology of renal tumors will permit earlier diagnosis and improved survival. The role of renal conserving surgery in the management of selected renal tumors is being evaluated at sev-

eral centers, as is the possible role of newer chemotherapeutic and immunologic agents in the management of recurrent or metastatic tumors.

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RFPs for Renal Research Sought

Approximately \$1 million in new grants will be awarded for kidney research worldwide in 1991 by Baxter Healthcare Corporation's Renal Division. November 15, 1991, is the deadline for submission of Requests for Proposals (RFPs) for the sixth round of its Extramural Grant Program (EGP).

Two categories of research will be funded in this round: 1) The Preservation of Residual Renal Function and 2) The Dialysis Patient and Nutrition.

"Baxter created this unique grant program in response to the limited funding of basic and clinical research and in answer to the widespread diversion of research funds to AIDS," said Lee Henderson, MD, FACP, Executive Director of Baxter's EGP. "Our goal is to stimulate scientific advances in the understanding of kidney disease and to ensure that related studies are properly funded."

Baxter has committed \$4.5 million in grants to 52 international researchers since the EGP began in 1989.

The RFPs are reviewed by a distinguished independent Medical Advisory Board comprised of the world's leading renal research scientists. Review criteria is based purely on the scientific merit of the proposed research.

Modeled after the National Institutes of Health research program, the EGP has two funding cycles per year. RFPs for this year's first cycle will be accepted until the April 12, 1991, deadline. The two categories to be funded in this additional round are 1) Beta₂-Microglobulin Amyloidosis and 2) Open category. The Open category offers scientists working in all areas of renal research the opportunity to submit grant requests.

For more information or to forward completed grant requests, contact Lee Henderson, MD, FACP, Executive Director, Extramural Grant Program at (708) 270-5200 or at Baxter Healthcare Corporation, Renal Division, Route 120 and Wilson Rd, Round Lake, IL 60073.

Trends in kidney procurement and transplantation in New York State

JOHN MENDELOFF, PhD; COLENE M. BYRNE, MA; RICHARD B. FREEMAN, MD

ABSTRACT. The growth in the number of Medicare patients with end stage renal disease (ESRD) in New York State receiving cadaver kidney transplants in the 1980s substantially lagged behind growth in the nation. Compared to the United States, New Yorkers on dialysis had less access to transplants. The greatest decline in transplant rates was experienced by New York's black population. During the early and mid-1980s, considerable transplant rate growth in New York City was maintained, despite very slow growth in local kidney procurement, by importing kidneys from other states, by residents seeking transplants elsewhere, and by a greater proportion of transplants going to Medicare ESRD patients. Since 1986, the number of kidneys procured in New York City increased while the number procured nationally fell. However, kidney imports to New York City dropped dramatically, and thus the number of cadaver transplants declined despite the growth in local procurement. Upstate, procurement and transplants started at a higher level, but grew even more slowly.

(NY State J Med 1991; 91:184-188)

In 1972, Congress extended Medicare benefits to all eligible US citizens with end stage renal disease (ESRD). Since then, the number of people beginning maintenance dialysis and receiving a kidney transplant has increased dramatically. Patients who have a successful transplant have a better quality of life and greater longevity than those who remain on dialysis.^{1,2} Transplantation is also less costly than dialysis after the first year.³

Despite these advantages, the number of cadaveric kidney transplants since 1986 has fallen slightly nationally and has fallen sharply in New York State. During the period of rapid increase in Medicare-funded transplants from 1981 to 1986, New York lagged somewhat behind the national pace. A closer examination of New York data indicates that the techniques used to keep the transplant rates of New Yorkers relatively high despite the slow growth in procurement no longer sufficed after 1986. These techniques included importing kidneys from other states, leaving the state to get transplants, and reducing the number of transplants performed on patients who

were not eligible for Medicare (eg, patients who were not US citizens). In this article, we describe in more detail the trends in cadaver kidney transplants of New York's ESRD patients and the closely related trends in cadaver kidney procurement, review their implications for access to transplants, and discuss possible explanations for this decline in New York.

The racial inequality in kidney transplantation is well documented⁴⁻⁷ and the decline in the availability of donor kidneys for transplantation has had a differential impact on black and white patients. Racial trends in cadaver kidney transplants are also examined in this study.

METHODS

Information on ESRD patients was obtained from the Health Care Financing Administration's (HCFA) Program Management and Medical Information System (PMMIS), including data on each patient who has received a transplant. The numbers of kidney transplants and of patients waiting for transplant were obtained from Medicare's annual facility surveys for 1981, 1983, 1985, 1987, and 1989 which cover both Medicare and non-Medicare patients. Some of the organ procurement organizations (OPOs) also provided data on kidney procurement. Estimates of the number of kidney transplants and patients waiting for a transplant in 1989 were obtained from the United States Renal Data Systems (USRDS) 1990 annual report⁸ for the United States and from the ESRD network of New York's 1989 Annual Report.⁹ Historical data on procurement and transplants in the New York City metropolitan area were obtained from the New York Regional Transplant Program's 1988 and 1989 Annual Reports.^{10,11}

The level of transplantation among different population groups was assessed by determining the numbers of cadaver kidney transplants performed per 1,000 patients under age 65 on dialysis, hereinafter called the transplant rate. All references to transplants in this study will refer to cadaver kidney transplants only, which comprise approximately 80% of all transplants.

Kidney procurement and transplant data are provided for the following New York State OPOs: the Upstate New York Transplant Services (UNYTS), which serves three transplant centers in Buffalo; the University of Rochester Organ Procurement Program; the Red-Cross-operated OPO in Syracuse, which merged with the Rochester program in early 1988; the Northeast Regional Transplant Program, operated out of the Albany Medical Center; and the New York Regional Transplant Program (NYRTP), which includes most of the hospitals in the lower Hudson Valley and in New York City. The numbers for two smaller downstate OPOs are included in the NYRTP figures: the Gift of Life OPO which procured organs from most of the hospitals in Brooklyn and some Manhattan hospitals until April of 1988 when it merged with the NYRTP; and the smaller hospital-based OPO operating out of State University of New York at

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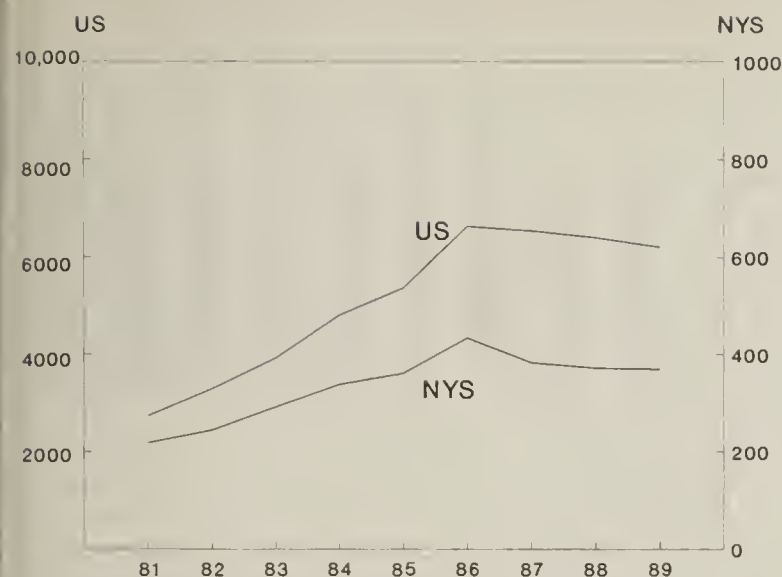


FIGURE 1. The number of cadaver kidney transplants performed on Medicare ESRD patients in New York State and in the United States from 1981 to 1989.

Stony Brook, which has operated independently from NYRTP since 1988. Unless otherwise noted, downstate refers to these three OPOs and the residents they serve. Upstate refers to the other four OPOs.

RESULTS

Between 1981 and 1985, the number of transplants funded by Medicare increased by 143% in the United States and 99% in New York State (Fig 1). The rate of transplants grew 57% nationally and 40% in New York (Fig 2).

Nationally, after this dramatic increase, there was a slight drop in Medicare transplants between 1986 and 1989 (6.4%). For New York Medicare patients, the number fell 14.7%. By 1989, New Yorkers on dialysis were 24% less likely than the national average to receive transplants, compared to 5% less likely in 1981. The relatively low growth rate in transplantation in New York patients is confirmed by comparing the number of transplants with a more direct measure of demand—the number of people who are on waiting lists for transplantation. Nationally from 1981 to 1987, growth in the number of patients on waiting lists for transplants almost matched the growth in the number of transplants performed (Table I). In New York, the ratio of waiting list patients to annual transplants

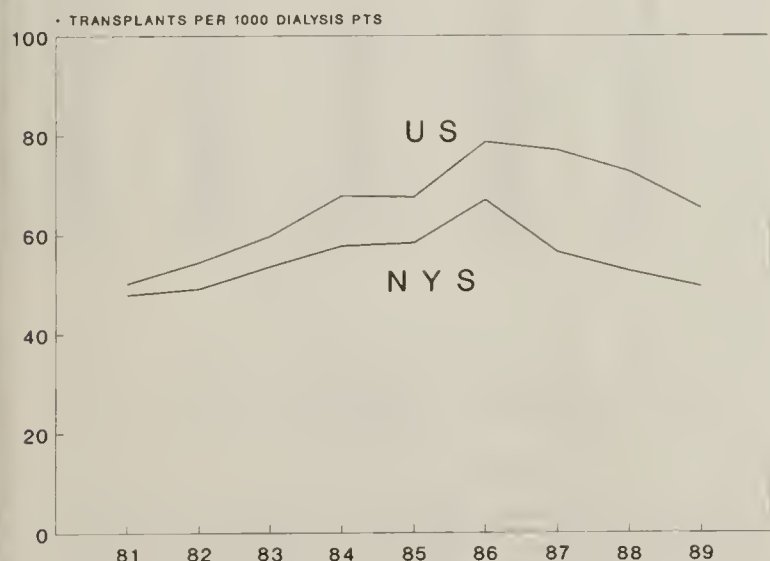


FIGURE 2. Rate of cadaver kidney transplants performed on Medicare ESRD patients in New York State and in the United States from 1981 to 1989. The rate is defined as the number of transplants performed for every 1,000 patients under the age of 65 who are Medicare dialysis patients.

TABLE I. Ratio of Patients* on Transplant Waiting Lists to the Number of Kidney Transplants, United States and New York State, 1981–1987

	1983	1985	1987	1989
United States	1.6	1.6	1.7	2.0
New York State	2.1	2.6	3.0	3.7

* Table includes Medicare and Non-Medicare patients.

grew sharply from 1.7:1 in 1981 to 3.7:1 in 1989.

Racial Trends in Cadaver Kidney Transplants. For the United States, the black transplant rate rose from 37.2 in 1981 to 46.4 transplants per 1,000 dialysis patients under age 65 in 1988 (Fig 3). For blacks on dialysis in New York, the transplant rate fell from 39.1 in 1981 to 31.1 in 1988. In New York, growth in the number of blacks receiving transplants between 1981 and 1989 lagged behind the growth in the number of whites receiving transplants. For the United States, the number of blacks and whites receiving transplants increased at a similar rate. For both the United States and New York State the number of blacks on dialysis grew much more quickly than the number of whites on dialysis. Blacks on dialysis in New York in 1981 were 5% more likely to receive a transplant than blacks nationally; by 1988, they were 33% less likely to receive a transplant.

Regional Trends in Transplants. New York dialysis patients who live in the counties served by the two New York City-based OPOs (downstate) made up approximately three-fourths of all dialysis patients under age 65 from 1981 to 1988. Downstate patients have had substantially lower transplant rates than residents who lived in the rest of the state (hereinafter referred to as upstate, although some upper Hudson Valley counties are included). The transplant rate for upstate residents has always exceeded the national rate by a substantial margin; yet the upstate advantage has been shrinking (Fig 4). In 1981, the upstate transplant rate was almost three times higher than the downstate rate; by 1988, it was only twice as high. By 1988, the number of transplants of upstate residents was only 36% higher than the 1981 level, compared to 102% higher downstate.

Procurement Trends.

Relation Between Transplants and Procurement. The average performance data on OPOs in New York State over the three-year period 1985–1987 shows major variations in procurement (Fig 5). Standardization of procurement was accomplished by calculating the procurement rate for each 100 hospital deaths of patients under age 65 due to head trauma or stroke for five New York State OPOs. Also indicated is the transplant rate per 100 patients under age 60 on dialysis for the same time period. The transplant rate is greatest in

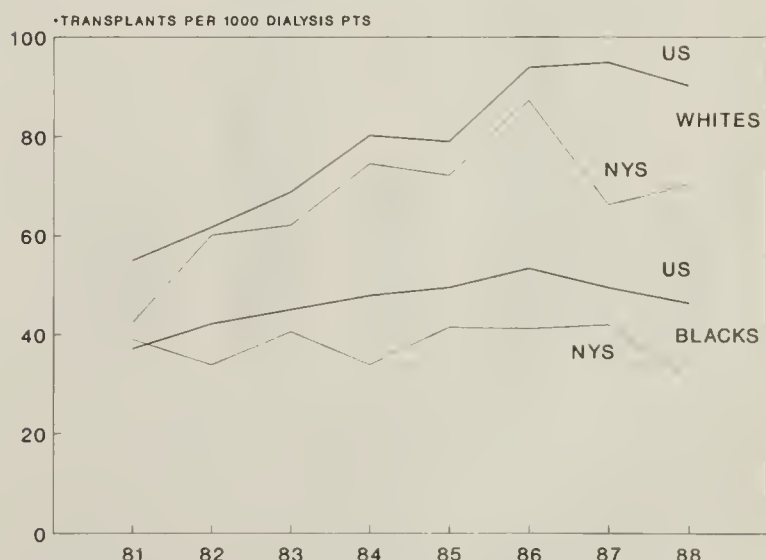


FIGURE 3. Cadaver kidney transplantation rate in New York State and in the United States by race from 1981 to 1988. The rate is defined as the number of cadaver kidney transplants performed for every 1,000 patients of that race under the age of 65 who are Medicare dialysis patients.

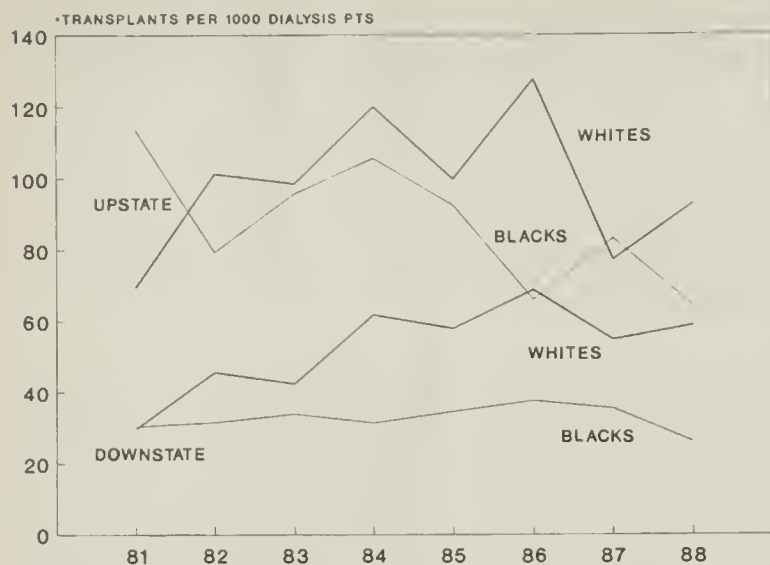


FIGURE 4. Cadaver kidney transplantation rate of upstate New York ESRD patients compared to downstate New York patients by race from 1981 to 1988. The rate of cadaver kidney transplants is higher in upstate New York than the national average. The transplant rate in blacks is lower than whites in both parts of the state. The rate of transplantation in blacks dropped in the latter part of the decade.

the two OPOs that have the highest procurement rate. Although the results that follow are presented for the downstate and upstate regions, it must be noted that there is considerable variation in the organ procurement performance of the upstate OPOs.

In downstate New York until 1989, the number of kidneys procured locally (from hospitals within the OPO) was always less than the total number of transplants performed (including both Medicare and non-Medicare patients) (Fig 6). From 1981 to 1986, local procurement in this region increased by only 9%, from 216 to 235, far below the rate of increase in Medicare-funded transplants.

The gap between total cadaver transplants and locally procured kidneys grew in the mid-1980s and then closed quickly after 1986 (Fig 6). This gap would be even larger if we considered that 5% to 10% of procured kidneys are discarded, either because suitable donors cannot be located quickly enough or because of problems with the kidneys. The third column in Figure 6 represents the number of

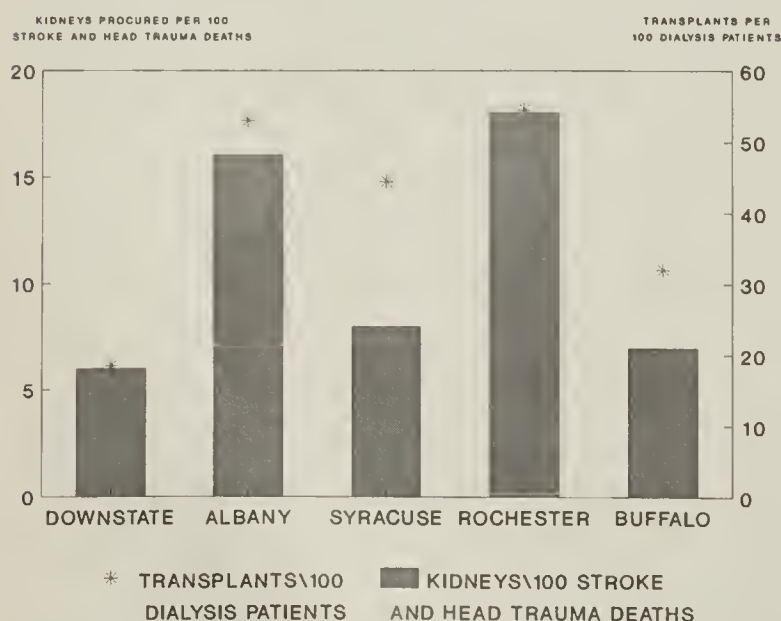


FIGURE 5. Average cadaver kidney procurement and transplant rate in each metropolitan area of New York State for the three-year period 1985 to 1987. The bars indicate the average number of cadaver kidneys procured per year per 100 deaths from head trauma and stroke in the area served by the local organ procurement agency. The asterisk represents the number of cadaver transplants performed for every 100 ESRD patients under age 60 undergoing dialysis in that area from 1985 to 1987.

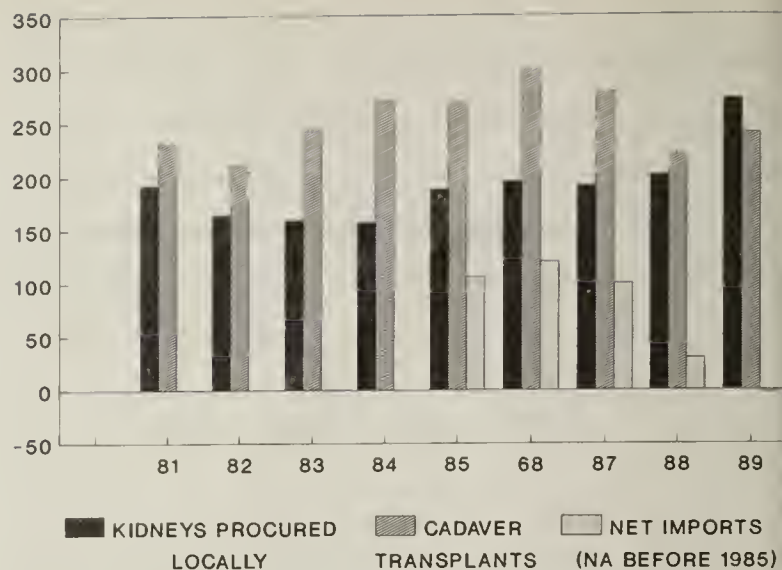


FIGURE 6. Number of kidneys procured locally, number of cadaver kidney transplants, and net imports of kidneys by downstate programs from 1981 to 1989. The solid bar represents cadaver kidneys harvested locally by organ procurement agencies; the cross hatched bar indicates the number of cadaver kidney transplants; and the stippled bar indicates the net imports into the area for the years 1985 to 1989. Data on imports are not available for 1984 and before. The number of organs procured exceeded the number of cadaver kidney transplants only in 1989 allowing for a net export of two kidneys.

net kidney imports (imports minus exports) from outside of the downstate region.

Of the kidneys imported for the downstate region by NYRTP and Gift of Life, the great majority came from other states. In 1985, only five of 122 imports came from other OPOs in New York State; in 1986, 16 of 107; in 1987, eight of 86; and in 1988, eight of 44.

Kidney procurement data for the four upstate New York OPOs are less complete, but it can be seen that local procurement far exceeded the number of transplants. The upstate OPOs exported many more kidneys than they imported. Local procurement actually decreased 13% from 1981 to 1985. Since 1985 local procurement has increased more slowly than downstate (Fig 7).

Trends in Factors Affecting Procurement. The great majority

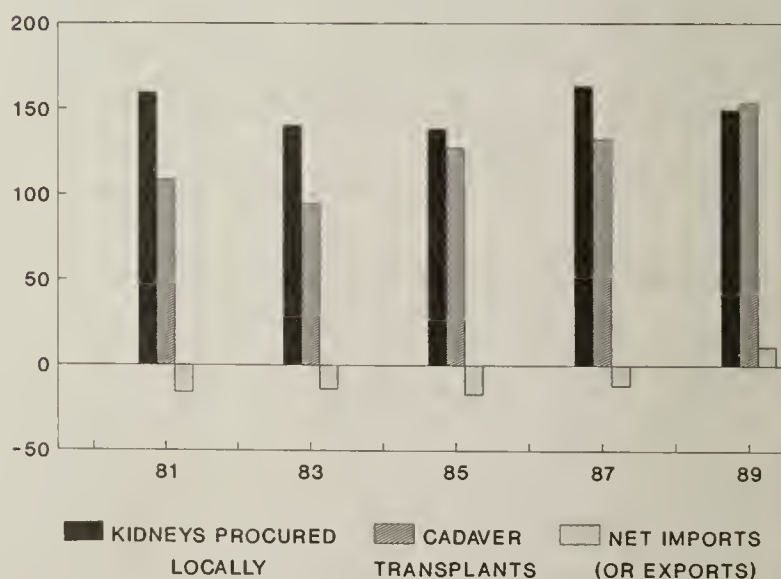


FIGURE 7. Number of kidneys procured locally, number of cadaver kidney transplants, and net imports of kidneys by the combined upstate New York programs from 1981 to 1989. The solid bar represents cadaver kidneys harvested locally by organ procurement agencies; the cross hatched bar indicates the number of cadaver kidney transplants; and the stippled bar indicates the net imports (or exports, below the baseline) to (or from) the area. The number of organs procured exceeded the number of cadaver kidney transplants in every year except 1989 which was the only year when there was a net importation of cadaver kidney organs.

of kidney donors die as a result of head trauma or cerebrovascular events. From 1981 to 1987, Vital Statistics data^{12,13} indicate that total deaths from motor vehicle accidents and homicides (the two major causes of head trauma deaths) declined more sharply nationally than in New York. For motor vehicles, the declines were 12% vs 9%; for homicides, 16% vs 11%. In both New York and the nation, stroke deaths dropped by 14%. By these measures, growth in organ procurement should have been less constrained in New York.

Consent rates for organ donation increased downstate in 1989, when 60% of donor family members consented to donation (Table II). All of the higher procurement downstate in 1989 can be attributed to this higher consent rate.

Migration of ESRD Patients Entering and Leaving New York for Transplants. The number of New York ESRD patients leaving the state to receive a transplant jumped sharply after 1982, from 8% of all residents' transplants to 19% in 1983 (Fig 8). The percentage then dropped steadily through 1987, and rebounded to 13% in 1988. In all except one of these eight years, the percentage of whites who received transplants out of state exceeded the percentage for blacks, usually by a large margin.

In 1981 and 1982, the number of Medicare-eligible ESRD patients coming to New York State for transplants exceeded the number of New Yorkers leaving the state for transplants (Fig 8). From 1983 through 1985, the two flows were almost equal because of the growing outflow. In 1986 and 1987, the outflow dropped and the inflow again became dominant. In 1988, for the first time, the out-migration substantially exceeded the in-migration.

The great majority of Medicare ESRD patients coming to New York received their transplants at downstate facilities. The percentage of Medicare-funded transplants in downstate New York that went to out-of-state residents dropped almost continuously from 1982 to 1988, from 36% to 12%.

Not all kidney transplants are funded by Medicare. Although nationally the estimate of non-Medicare kidney transplants has ranged around 10%, in New York City the proportion has been much higher, probably because of a large number of foreigners and patients lacking the work history needed to be eligible for Medicare. It is unclear how many of these recipients were New York residents who were not eligible for Medicare and how many were non-New Yorkers, including non-citizens (eg, foreign nationals and illegal aliens) who had come to New York to get transplants. Non-Medicare patients accounted for an average of 24% of all downstate transplants from 1981 to 1983, but only 11% from 1986 to 1988.

DISCUSSION

Kidney transplantation has been accepted treatment for ESRD for over 20 years and has proven to be successful and cost saving compared to dialysis. Nationally and in New York State, the supply of cadaver kidneys has not kept pace with the number of ESRD patients waiting for a transplant. This deficit occurred despite public policies implemented to enhance organ retrieval for transplantation. These policies include the Required Request Law, which became effective in New York in 1986.

Clearly, the number of transplants nationally is con-

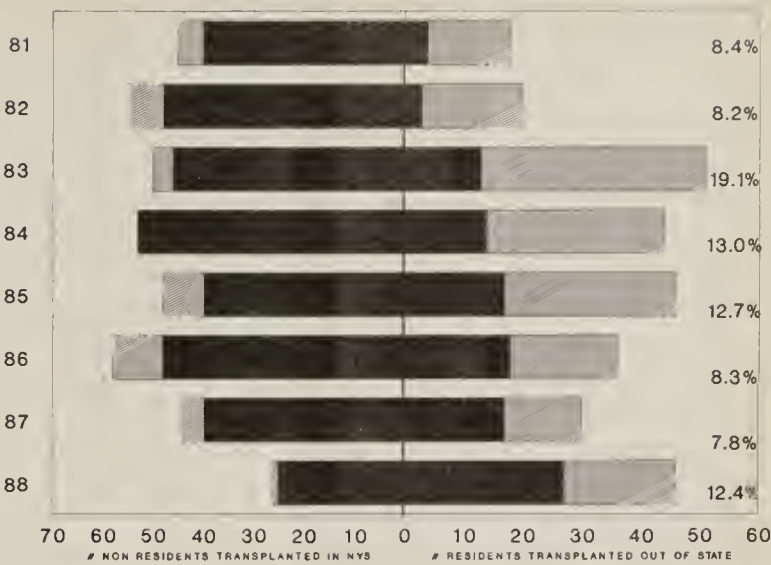


FIGURE 8. Medicare ESRD patient migration to and from New York State for kidney transplantation from 1981 to 1988. Migration of out-of-state residents into New York is shown on the left and of New York residents out of the state is depicted on the right. The solid bar represents downstate migration and the cross hatched bar indicates upstate movement. The figures in the column on the right indicate the percent of all New York transplant patients who went out of state for their transplants. See text for further description.

strained by the number of organs procured. However, a sizeable growth in Medicare-funded transplants for downstate New York residents took place up until 1986 despite very limited growth in local kidney procurement in that region. A number of factors allowed the number of Medicare-funded transplants for downstate residents to grow much faster than local kidney procurement. The first factor, kidney imports, is least well described by the data presented here because import data were not available before 1985. By 1985, the downstate region was a very large net importer of kidneys. It seems very likely that after 1982 the downstate OPOs increased their imports from other regions where procurement rates were increasing more rapidly. After 1986, when procurement ceased to grow in other states, net imports plummeted. Since organ procurement actually grew downstate after 1986, all of the reduction in transplants downstate after 1986 can be accounted for by this drop in imports.

A second factor cushioning downstate New York's dialysis patients from the slow increase in locally procured kidneys was growth in their numbers leaving the region for transplants. Most of this growth was to out-of-state transplant centers, rather than to other areas of the state.

The third cushion for New York State's Medicare ESRD patients was provided by the reduction in the number of transplants for those who were not Medicare-eligible New York State residents. A part of this drop may reflect expanded enrollment in the Medicare ESRD program since the early 1980s; however, even among Medicare eligibles, there was a definite shift toward state residents at downstate facilities. One explanation for this shift could be that the growth in transplant waiting lists in New York encouraged non-residents to look outside New York State for centers with shorter waiting lists.

In upstate New York, procurement rates have varied widely among OPOs, but also usually failed to keep pace

TABLE II. Medically Suitable Organ Donor Referrals and Donations, NYRTP, 1987-1989

	1987	1988	1989
Referrals	471	484	545
Medically rule out	238	252	310
Medically suitable rate	49%	52%	43%
Potential organ donors	233	232	235
Consent to donation	101	106	140
Consent rate	43%	46%	60%

Source: NYRTP 1989 Annual Report.

with national trends. In upstate New York a possible explanation for the growth in procurement is that the procurement rate had reached such a high level that further gains were very difficult to achieve. Although not all medically suitable donors are identified and referred for donation, a recent study suggests that the number of organs that could "reasonably be expected" to be procured is much less than earlier estimates had indicated¹⁴ and that some OPOs were approaching their potential organ donor rate.¹⁵ Even short of that point, it is plausible that the extra effort required to procure each additional organ was increasing rapidly. For example, OPO procurement staff must develop relations with smaller hospitals to increase referrals, each of which is unlikely to contribute very much to the overall procurement effort.

Given that the procurement rate downstate is lower than upstate, it seems less likely that the slow growth downstate could reflect approaching exhaustion of the potential donor pool. However, New York City always has had demographic factors that have limited the donor pool. These include a low death rate from motor vehicle accidents and a high percentage of potential donor deaths occurring among blacks and other minorities who are less likely to donate organs.^{10,16-18} Because these are long-standing features of New York City, they cannot by themselves explain a slow rate of growth in local procurement, unless the pool really was near exhaustion. Other possible explanations for the slower growth in local procurement for downstate New York up until 1986 include: less growth or a greater drop in medically acceptable potential donors; less growth or a greater decline in the preferences of families regarding donation; and relative deterioration of the organ procurement process, as hospitals failed to make referrals and OPO staff failed to convince families to allow donation.

We lack any good evidence on comparative trends for the latter two factors. However, it is noteworthy that the consent rate jumped sharply in 1989, suggesting improved performance by the OPO there.

Regarding trends in medically acceptable donors, death rates for the relevant causes of death for organ donation have not declined more sharply in New York City than in the rest of the state. One distinctive factor about New York City is the size of the acquired immunodeficiency syndrome (AIDS) epidemic. The presence of human immunodeficiency virus (HIV) antibodies is always a contraindication for organ procurement. Data from the Gift of Life OPO show that, among those who were formally referred for donation, "high risk for HIV infection" did not become a significant cause of medical unsuitability until 1987.¹⁸ In 1987 and 1988, the numbers of referrals excluded for that reason were six or seven each year. On a city-wide basis, these numbers would probably be two to four times higher than those from the Brooklyn-based program. However, many of these organs would not have been donated even in the absence of HIV, either because

of other donor risk factors or because of a refusal to donate. On the other hand, it is possible that concern about possible HIV infection has reduced the number of referrals, generating an effect that goes beyond that captured by looking only at HIV infection among referrals. Further research is needed to estimate the potential pool of medically suitable donor kidneys downstate.

It is encouraging that kidney procurement in downstate New York has actually been growing faster since 1986 than in the rest of the nation. However, because the region was simultaneously being weaned from its dependence on imports, transplants grew very little. This is the opposite of the pattern before 1986 when transplants grew substantially despite little growth in procurement.

The link between organ procurement rates and kidney transplant rates makes geography an important determinant of the chances that a person on dialysis will be able to receive a transplant. We found that this relationship was confounded somewhat in downstate New York, and that Medicare ESRD patients' transplant rates increased despite a slow growth in procurement. However, most of the gains within the downstate region accrued to whites and the transplant rate of blacks fell compared to whites. The reasons for that pattern also require further study.

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Effective hypertension control in inner city blacks

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GURUSWAMY RAMAMURTHY, MD

ABSTRACT. A clinic for patients with "resistant" hypertension was established and patients were followed by one physician, nurse, and secretary. The records of 105 randomly chosen patients out of 700 were reviewed. In 86 of 105 (82%), diastolic blood pressure was controlled (<90 mm Hg) (group I), but in 19 patients, after 54 ± 6 (mean $\pm$ standard error) months, it remained >90 mm Hg (group II) with substantial improvement in 53% (10 of 19 patients). The two groups were similar in age (57 ± 1 vs 54 ± 3 years), race (84% vs 74% blacks), and sex (75% vs 86% female). The entry blood pressures in groups I and II were similar, $170 \pm 3/101 \pm 1$ and $167 \pm 6/105 \pm 3$ mm Hg, respectively. Last visit blood pressure was $130 \pm 1/79 \pm 1$ in group I, lower than $156 \pm 5/94 \pm 2$ in group II ($p < 0.05$). At entry into the clinic and at the last visit, dosing and type of medications were similar in both groups. Although patient visits averaged 6.7/yr in both groups, patients in group II missed 1.7 ± 0.3 compared with 0.9 ± 0.1 visits/year for group I ($p < 0.01$). Group II patients were also less compliant with medications, primarily because of psychosocial problems. Medications, however, were more available to this group, since 16 of 19 (84%) were Medicaid recipients, compared with 46 of 86 (53%) in group I ($p < 0.025$).

These data indicate that a high control rate of hypertension can be achieved in inner city, mostly black patients when treated in a specialized clinic. There is a hard core group that remains uncontrolled due to noncompliance with medication regimens unrelated to drug availability or clinic structure.

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Of the estimated 58 million Americans who have hypertension, 7 million are black. The prevalence of hypertension is clearly greater in blacks than in whites. Specifically, blacks have rates of mild and moderate hypertension that are two times that of whites, and, in even sharper contrast, the rate of severe hypertension (diastolic blood pressure 115 mm Hg or greater) is five to seven times higher in blacks.¹ Moreover, at any given diastolic blood pressure, blacks have a greater mortality rate from cere-

brovascular disease compared with whites, making treatment of these hypertensive patients particularly urgent.²

A recent survey of Medicare end stage renal disease (ESRD) patients demonstrated that 30% are black, almost three times that expected from the number of blacks in the general population (11%-12%). The ratio of blacks to whites reaching ESRD secondary to hypertension was 17:1 in the 25-44-year age group and 11:1 in the 45-64-year age group.³ It has been suggested that the disproportionately greater risk of ESRD among black hypertensives reflects, at least in part, the severity and inadequate control of hypertension in this population.³ Control of blood pressure in black hypertensive patients, however, does lead to a dramatic reduction in all causes of mortality.⁴

Since the prevalence of hypertension in blacks is highest among those with low socioeconomic status, providing effective care to the inner city indigent black population is a major public health challenge.⁴ The availability, per se, of medical care may not be adequate to achieve a high control rate in this population, in which complex practical and psychosocial problems often preclude effective antihypertensive therapy.^{5,6} Many of these patients fail to comply fully with their therapeutic regimens or else completely drop out of treatment.⁷ Although true pharmacologic resistance is rare, many inner city blacks are prematurely and incorrectly labeled as "resistant" hypertensives, and more intensive efforts to control their blood pressure are often abandoned.^{6,8} Many difficult patients are refractory to conventional management but may respond to a structured and specialized approach, which overcomes difficult logistic and psychosocial barriers to treatment.^{6,9,10}

In 1981, in order to provide effective care specifically for "resistant" hypertensives in a predominantly black inner city community, we formed a specialized hypertension clinic. Our method of providing health care and the results obtained form the basis of this report.

PATIENTS AND METHODS

Approximately 700 patients were recruited from the general medical clinic at The Brookdale Hospital Medical Center, the hospital's emergency room, and, rarely, from community referral. The majority of patients were selected by us after we reviewed their medical clinic charts. Despite long term follow-up, usually by different health care providers, these patients' hypertension remained uncontrolled (diastolic blood pressure greater than 90 mm Hg). All were taking two or more drugs, and several required emergency room visits for uncontrolled symptomatic hypertension in spite of active therapy.¹¹ More mild, borderline-

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controlled hypertensives on a single drug or a nonpharmacologic regimen were excluded.

In contrast to the care received in the general medical clinic, these selected patients were followed in our clinic by a single physician with specialized training in hypertension, and by a single nurse. In addition, a clinic secretary tracked broken appointments, and arranged laboratory testing and appointments with social service. Psychiatric care was provided when necessary. These measures were designed to ease logistic and social constraints precluding effective therapy. To insure the availability of all laboratory and drug regimen data at each contact, a hypertension clinic chart separate from the hospital clinic chart was kept on file for each patient. Waiting time for each visit was kept at a minimum (rarely exceeding 30 minutes) by restricting the number of patients seen at each clinic session. Each patient was separately counseled by the physician and nurse regarding the consequences of untreated hypertension, with specific emphasis on the need to comply with medication and diet. Frank discussions were encouraged to review the issues interfering with therapy. Although no formal education classes were held, relevant literature about hypertension was given to patients when requested or considered useful.^{12,13}

Patients were informed of their blood pressure readings at each visit, and the goals of therapy were clearly outlined.¹⁴ Written instructions were frequently given to patients and their families. Family members were encouraged to participate in patient care by involving them in food preparation to achieve sodium restriction and weight loss and with medication compliance issues, when necessary.¹⁵ All classes of antihypertensive medications, including minoxidil and guanethidine, were utilized, usually in a once-a-day or twice-a-day regimen.^{16,17} The physician readily changed a patient's drug regimen to avoid side effects.¹⁴ Frequent follow-up appointments were given,¹⁸ and patients were instructed to communicate with staff members regarding any problems that arose subsequent to their visit. For this purpose, a direct telephone number was made available to all the patients, eliminating the need to wait for the hospital operator or central clinic receptionist. A missed appointment was followed by a phone call⁷ which was accepted by the patient as an expression of our concern rather than a punitive measure. The methods described above were designed to foster a close relationship between the patient and all members of the health care team. This relationship was considered an indispensable part of treatment.^{9,19,20}

To date, we have analyzed 105 charts randomly selected from the approximately 700 patients seen in our clinic over a nine-year period. Statistical analysis was carried out by the Student's paired t-test, with $p < 0.05$ considered significant.

RESULTS

Blood pressure control was defined as a sitting diastolic blood pressure (DBP) of less than 90 mm Hg on three separate occasions. Accordingly, 86 of 105 patients (82%) were controlled (group I), with DBP decreasing from 101 ± 1 mm Hg on entry to 79 ± 1 mm Hg at last visit ($p < 0.0001$). Nineteen patients (18%) remained uncontrolled (group II), but at the end of 54 ± 6 months of follow-up, this group had a significant decrease in DBP from 105 ± 3 mm Hg on entry to 94 ± 2 mm Hg ($p < 0.001$) (Fig 1). The significant decrease in DBP in this group was primarily due to ten patients (9.5%), who had a decrease in DBP greater than 10 mm Hg, or a decrease to less than 95 mm Hg (partial control). For the whole group, DBP decreased in these ten patients from 112 ± 3 mm Hg at entry to 92 ± 1 mm Hg ($p < 0.001$) (Fig 2). Thus, complete and partial control was achieved in 96 patients (91.5%). The nine patients who were totally resistant to various drug regimens had virtually no change in DBP, which was 98 ± 4 mm Hg at entry and at last visit. These patients were thought to be poorly compliant or totally noncompliant. Seven had significant psychosocial problems which were felt to be the main barriers to successful therapy. Three were under psychiatric care.

There were no striking demographic differences between group I and group II. Most patients were female: 75% in group I and 86% in

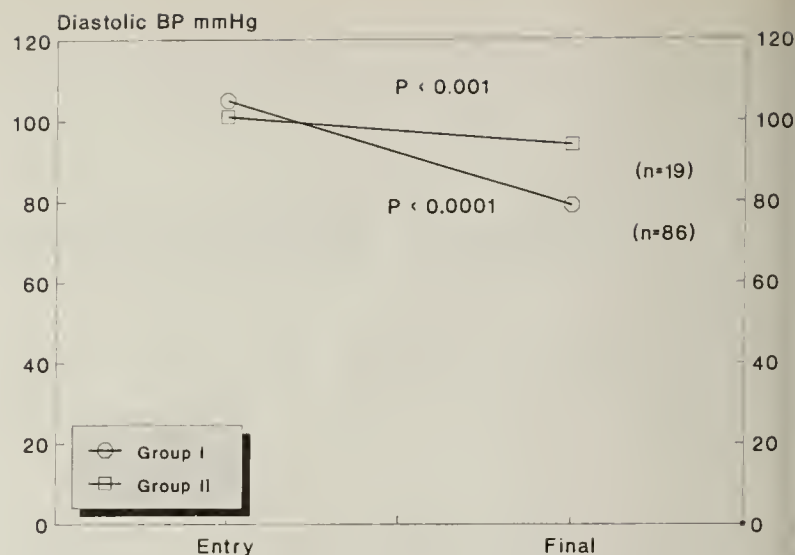


FIGURE 1. Diastolic blood pressure in both groups at entry and at final visit.

group II. Eighty-four percent of the patients in group I were black compared with 74% in group II; 10% in group I were Hispanic compared to 26% in group II; 6% in group I were white compared to none in group II (Fig 3). The mean age in group I was 57 ± 1 years compared with 54 ± 3 years in group II. Additionally, body weight, types of antihypertensive medications, dosing intervals (usually once a day or twice a day), and incidence of concomitant illnesses were similar in the groups both at entry and at last follow-up. It should be emphasized that in addition to similar demographics and overall medical approach, patients in both groups received the same counseling and one-on-one time with the physician and nurse at each visit.

Although not used to define blood pressure control, the effect of therapy on systolic blood pressure (SBP) was also evaluated. Entry SBP in group I and II was similar, 170 ± 3 mm Hg and 167 ± 6 mm Hg, respectively. Only group I showed a significant reduction to 130 ± 1 mm Hg ($p < 0.0001$), a decline of 40 mm Hg. Group II SBP fell less dramatically to 156 ± 5 mm Hg (Fig 4).

Despite the fact that DBP and SBP were similar in both groups at entry, the uncontrolled group had a higher incidence of end organ damage (95%) compared with the controlled group (66%) ($p < 0.025$). This was determined by the presence of one or more of the following: hypertensive retinopathy, nephrosclerosis, electrocardiographic evidence of left ventricular hypertrophy, or a history of a cerebrovascular accident.

Group II patients missed 25% of scheduled visits, whereas group I missed only 13% ($p < 0.05$). Although it is difficult to quantitatively assess compliance with drugs, since pills were not counted, the uncontrolled group was felt by the staff to be less compliant with medi-

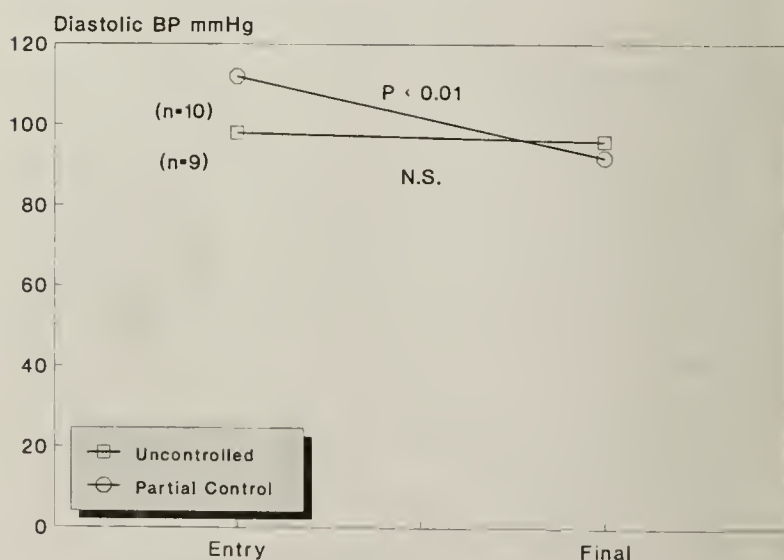


FIGURE 2. Diastolic blood pressure in group II patients divided into uncontrolled and partially controlled subgroups, at entry and final visit.

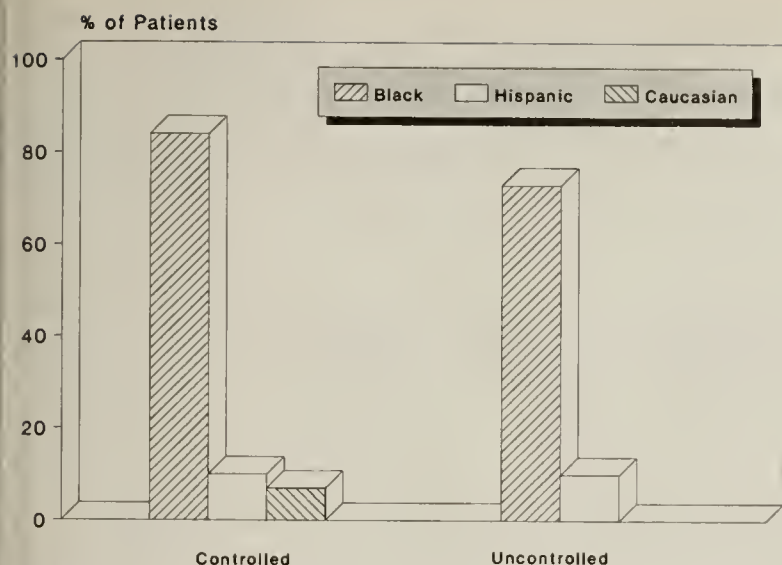


FIGURE 3. Ethnic distribution of 105 study patients in controlled and uncontrolled group.

cations as well as appointments. This poor compliance appeared not to relate to the cost of medications, since 84% (16 of 19) of group II were Medicaid recipients who did not pay for drugs. In contrast, only 53% of group I were Medicaid recipients.

DISCUSSION

Uncontrolled hypertension in the inner city poses a major public health problem. Effective hypertension control in this population is difficult in the usual therapeutic setting, and requires a carefully structured specialty clinic.^{6,7,21,22} Other investigators have described their successful efforts in controlling hypertension in inner city patients, but insufficient data were given regarding previous therapy to define these patients as "resistant."^{6,21,22} Unlike these projects, we specifically designed our clinic to provide effective therapy for "resistant" hypertensive patients. This specialized approach was offered primarily to patients who failed to respond to therapy while attending the hospital's general medical clinic. These patients had uncontrolled hypertension despite long term follow-up and pharmacologic therapy with at least two drugs. We designed our clinic to eliminate the impersonal and confusing environment of a general medical clinic and incorporated those features previously shown to be most effective for blood pressure control.^{6,7,9,10,12-15,22}

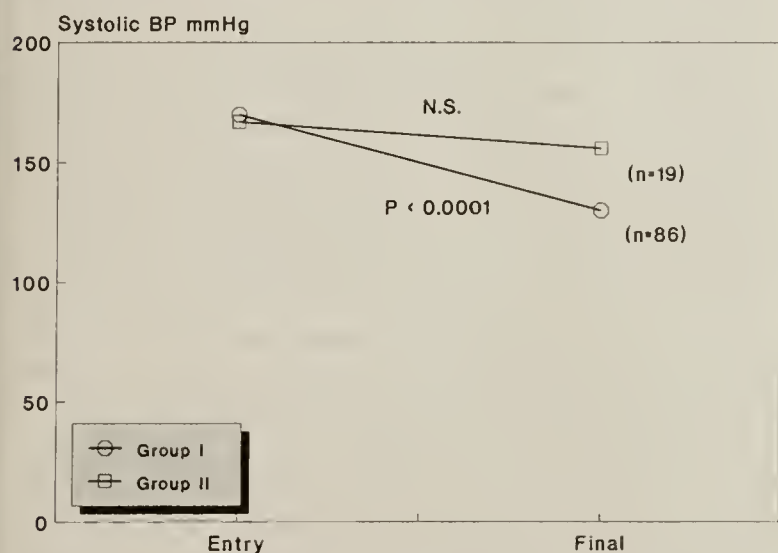


FIGURE 4. Systolic blood pressure at entry and final follow-up in group I (controlled) and group II (uncontrolled).

By utilizing this multifaceted approach, we were able to achieve an 82% control rate (91.5% including partial control) in this select group of hypertensive patients in whom previous therapy had failed.

Nineteen patients remained uncontrolled, although they were similar to the control group with regard to age, sex, body weight, racial distribution, types of antihypertensive regimens used, concomitant illnesses, and entry systolic and diastolic blood pressure. The uncontrolled group, however, had a higher incidence of missed appointments and end organ damage, indicating poor compliance and either more severe hypertension and/or a longer uncontrolled course.

Some investigators have suggested that cost of drugs is a major obstacle to blood pressure control,¹⁵ while others have not confirmed this finding.²¹ In this study, 84% of the uncontrolled group were Medicaid recipients who received their drugs without charge, while only 53% of the controlled group had Medicaid. In neither group were there patients who had other drug insurance programs. These data suggest that in this patient population poor control (poor compliance) was not due to the cost of medication.

In summary, we were able to achieve a remarkably high blood pressure control rate among inner city, predominantly black, hypertensive patients by providing a well-structured, organized clinic in which personalized care was emphasized. Based on our review of approximately 15% of the clinic population, only 9% of the patients had no obvious benefit from even this therapeutic environment, suggesting that there is a small group of patients whose blood pressure cannot be controlled, most likely due to noncompliance with therapy (diet and drugs), which does not appear to be related to the cost of drugs.

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Lipid abnormalities in black renal patients

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ABSTRACT. Racial differences in lipoprotein (LP) and cardiovascular (CV) abnormalities have been noted in the general population and in the population of patients on dialysis. Few studies have investigated the interaction of race and LP and CV disturbances in other renal disease groups. We studied lipid profiles and risk ratios (total cholesterol (TC)/high density lipoprotein-cholesterol (HDL-C) and apolipoprotein (apo) A-I/apo B (A-I/B)) and the influence of race across a spectrum of renal disease groups (normal renal function (NRD), nephrotic range proteinuria (NS), hemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD), post-transplant (TR), renal insufficiency (RI)). We also performed a longitudinal study of lipid profiles in patients with end stage renal disease (ESRD) and the relationship of these profiles to race and other variables.

There was a general tendency towards a better CV risk profile for blacks than whites in all the groups. Blacks tended to have lower TC, higher HDL-C, lower TC/HDL-C, higher apo A-I, lower apo B, and higher A-I/B.

We analyzed four yearly cross-sections of the HD and CAPD populations using ANOVA with adjustment for appropriate covariates. Whites had lower HDL-C and a higher TC/HDL-C risk ratio than blacks. HD patients had lower TC, TC/HDL-C, apo A-I, and apo B than CAPD patients, and women had higher TC than men. When lipid profiles were studied longitudinally by yearly intervals, no consistent significant changes were seen, but over two years, levels of apo B fell and A-I/B rose. Race had no significant effect on any of the longitudinal data. We conclude that race, gender, and dialysis modality all exert significant effects on the lipid profiles of ESRD patients. The favorable effect of black race on the lipid profile may explain the reduced incidence of coronary disease and mortality in blacks with ESRD despite their increased incidence of hypertension.

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Lipoprotein and cardiovascular risk ratios differ by race. Tyroler et al¹ noted that blacks have lower plasma triglyc-

erides, lower low-density lipoprotein-cholesterol (LDL-C) and higher high-density lipoprotein-cholesterol (HDL-C) than whites, especially for males. Tyroler et al also reported that whites had lower apolipoprotein (apo) A-I than blacks, but that this did not totally explain the HDL-C difference seen, indicating a possible racial difference in the lipoprotein composition.¹ Furthermore, there is a greater prevalence of coronary disease and cardiovascular mortality in the white population.^{2,3}

Lipoprotein and cardiovascular abnormalities are highly prevalent in patients with chronic renal insufficiency and end stage renal disease (ESRD),⁴⁻⁶ and cardiovascular disease is the most important cause of mortality in ESRD.⁷ Some of the lipid disturbances that have been identified in the uremic population include hypertriglyceridemia in most patients, reduced HDL-C in hemodialysis (HD) and pre-ESRD patients, and increased total cholesterol (TC) in patients on continuous ambulatory peritoneal dialysis (CAPD).⁸⁻¹⁵ Enzyme activities are depressed in this population, notably lipoprotein lipase, hepatic lipase, and lecithin cholesterol acyl transferase (LCAT).^{10,16,17} Apo C-III is increased,¹⁸ lipoprotein composition (eg, HDL-C/apo A-I) is abnormal,^{9,19,20} there is an increased prevalence of an abnormal pre-beta lipoprotein (possibly representing the atherogenic intermediate-density lipoprotein, IDL),^{10,21} and the TC/HDL-C ratio is increased.^{8,9,17,20}

Accelerated atherosclerosis is believed to be a consequence of ESRD.^{4,5} However, it may be more likely that the development of coronary disease in the ESRD population largely precedes the onset of end stage disease and is, perhaps, the result of the lipid disturbances of renal insufficiency. Alternatively, dyslipidemia may contribute to the genesis or progression of renal insufficiency as well as coronary disease.²² A variety of investigations have been unable to link any particular lipoprotein disorder to cardiovascular disease in uremia.^{23,24} Similarly, clinical, angiographic, and autopsy studies do not support the concept of accelerated atherosclerosis in ESRD.²⁵⁻²⁹

Lipid abnormalities have been studied in various other groups with renal disease. For example, patients with nephrotic syndrome usually have marked hypercholesterolemia with elevated LDL-C and very low density lipoprotein-cholesterol (VLDL-C), but HDL-C may be low, normal, or high.³⁰ Patients who have had a renal trans-

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plant have hypercholesterolemia, but HDL-C levels do not rise proportionately to total cholesterol.^{8,31}

Only a few studies have investigated the interaction of race, and lipid and cardiovascular disturbances for the various renal disease groups. Rostand et al²⁵ reported an increase in new-onset ischemic heart disease in whites relative to blacks on HD. Goldberg et al¹² reported that white HD patients had lower levels of HDL-C, apo A-I, and apo A-II than blacks, and that white men had increased triglycerides and abnormal distribution of HDL subfractions. This may explain the increase in cardiovascular disease in white ESRD patients, despite the increase in hypertension and left ventricular hypertrophy (LVH) seen in the black population.²⁵⁻²⁷

Lipid profiles and risk ratios across a spectrum of renal diseases were studied and analyzed for the influence of race. Additionally, a longitudinal study of the natural history of lipid disturbances in ESRD and its relationship to race and other variables was performed.

PATIENTS AND METHODS

The following six groups of patients were included in Study I:

- NRD—17 subjects with normal renal function, including 11 medical clinic patients and 6 volunteers (creatinine range, 0.7 to 1.5 mg/dL);
- NS—13 patients with nephrotic range proteinuria (greater than 4 g/day) (creatinine range, 0.9 to 5.5 mg/dL);
- HD—101 patients maintained by hemodialysis (HD);
- CAPD—25 patients maintained by continuous ambulatory peritoneal dialysis (CAPD);
- TR—11 patients who had received kidney transplants (TR) six months to 14 years earlier;
- RI—5 renal clinic patients with moderate renal insufficiency (RI) but without nephrotic range proteinuria (creatinine range, 3.3 to 5.9 mg/dL). This group was not analyzed by race, owing to small sample size.

For Study II, an evolving cross-section of 281 patients maintained by HD or CAPD was studied from 1987 to 1990.

Clinical data and history for each patient included the following: age, gender, race, etiology of ESRD, duration of ESRD and months undergoing dialysis, weight, type of dialytic therapy, dialyzer membrane, dialysate, medications, history of peripheral vascular disease, coronary disease, cerebrovascular disease, hypertension or liver disease.

Venous blood samples were drawn (pre-dialysis for HD), and the following determinations were carried out: 1) HDL-C (assay by EM Diagnostic Systems, Gibbstown, NJ, on DuPont ACA, Wilmington, DE) (reference range, 32 to 96 mg/dL); 2) TC (SMAC autoanalyzer, Technicon, Tarrytown, NY) (reference range, 120 to 200 mg/dL); 3) apo A-I (immunoturbidimetric assay, Isolab Inc, Akron, OH) (reference range, 100 to 170 mg/dL); 4) apo B (see apo A-I) (reference range, 60 to 100 mg/dL); 5) intact PTH (Allegro Intact PTH, Nichols Institute, San Juan Capistrano, CA) (reference range, 10 to 65 pg/mL); and 6) multiphasic biochemistry screen (SMAC autoanalyzer, Technicon, Tarrytown, NY). Atherogenicity risk ratios were computed from the lipid and apo levels (TC/HDL-C and apo A-I/apo B (A-I/B), respectively).

Group means were compared using Student's t-test and one-way ANOVA, after stratification by race (Study I) and by race, gender, and dialysis modality (Study II). Analysis of covariance was used in Study II to further adjust for case mix variables, using SPSS statistical software. Results are reported as mean $\pm$ standard error of the mean (SEM).

RESULTS

Study I. The clinical, biochemical, and lipid parameters for the renal disease groups studied are summarized in Figure 1 and in Ta-

bles I and II. There is a general tendency towards a better cardiovascular risk profile for blacks than whites in all the groups (Figs 2 and 3, Table II). TC was lower in blacks, especially in the CAPD group ($p < 0.1$). Blacks had significantly higher HDL-C ($p < 0.1$ for NRD, $p < 0.01$ for HD) except for the CAPD and TR groups. TC/HDL-C was lower in blacks ($p < 0.001$ for HD) except for the TR group. Apo A-I was higher in blacks ($p < 0.05$ for HD) except for CAPD patients. Apo B was lower in blacks ($p < 0.01$ for HD) except for TR patients. A-I/B was higher in blacks ($p < 0.01$ for HD).

Study II. The case mix variables for the four evolving cross-sections of ESRD patients studied from 1987 to 1990 can be seen in Table III. Table IV contains an analysis of the lipoprotein profile of a typical annual cross-section (1989) stratified by race and dialysis modality.

Serial cross-sections were analyzed by ANOVA to determine the influence of race (Hispanics excluded) with adjustment for age, gender, months on dialysis, dialysis modality, and diabetic status. We also assessed the influence of gender and of dialysis modality using ANOVA with appropriate covariates. Whites had lower HDL-C ($p < 0.05$) and higher TC/HDL-C ($p < 0.05$) than blacks. HD patients had lower TC ($p < 0.001$), TC/HDL-C ($p = 0.05$), apo A-I ($p < 0.01$) and apo B ($p < 0.01$) than CAPD patients, and women had higher TC ($p < 0.001$) than men.

When studied longitudinally by yearly intervals (paired t-test), there were no consistent significant changes seen for TC, HDL-C, apo A-I, apo B, or their ratios, despite some one-year fluctuations. Over two years (paired t-test), apo B fell ($p < 0.001$) and A-I/B rose ($p < 0.05$). Race had no significant effect on any of the longitudinal data.

The preliminary analysis of lipid profiles for non-survivors for the period 1987 to 1990 revealed that there was no significant effect of race on lipid parameters. For whites and not blacks, however, there was a tendency to lower HDL-C values in non-survivors with coronary disease or coronary death.

DISCUSSION

In this study, there was a general tendency towards a better cardiovascular risk profile for blacks than whites in all the groups. TC was lower in blacks, especially in the CAPD group. Blacks had higher HDL-C except for CAPD and TR patients, and a lower TC/HDL-C except for the TR group. Blacks had higher apo A-I except for CAPD patients, lower apo B except for TR patients, and a higher A-I/B.

When we analyzed the four yearly cross-sections of the HD and CAPD populations by ANOVA with covariance to determine the influence of race, we found that whites had lower HDL-C and higher TC/HDL-C than blacks. In

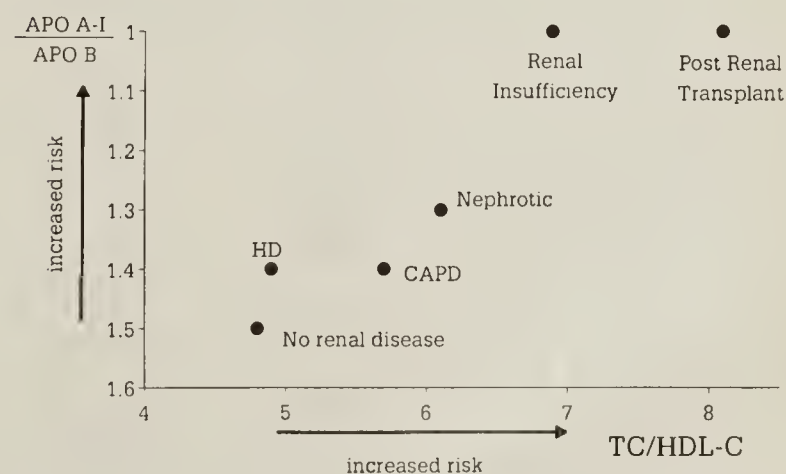


FIGURE 1. Mean atherogenic risk ratios; total cholesterol (TC)/high density lipoprotein-cholesterol (HDL-C), and apolipoprotein (apo) A-I/apo B for the renal groups (HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis).

TABLE I. Clinical and Biochemical Parameters for Renal Groups* (Study I)

	NRD	NS	HD	CAPD	TR
N	17	13	101	25	11
Females	11	6	53	12	1
Males	6	7	48	13	10
Whites (W)	6	4	23	5	4
Blacks (B)	6	7	59	19	6
Hispanics	5	2	19	1	1
Non-diabetic	14	7	68	19	7
Diabetic	3	6	33	6	4
Age (yr) (mean $\pm$ standard error of the mean)					
W	43 $\pm$ 5	41 $\pm$ 12	58 $\pm$ 4	58 $\pm$ 8	30 $\pm$ 2 [†]
B	55 $\pm$ 6	54 $\pm$ 5	56 $\pm$ 2	52 $\pm$ 3	48 $\pm$ 2
Weight (lb)					
W	189 $\pm$ 19	137 $\pm$ 39	138 $\pm$ 6 [†]	139 $\pm$ 19	167 $\pm$ 10
B	191 $\pm$ 12	161 $\pm$ 11	152 $\pm$ 5	158 $\pm$ 8	178 $\pm$ 14
Systolic blood pressure					
W	127 $\pm$ 4	108 $\pm$ 10	135 $\pm$ 4	122 $\pm$ 12	145 $\pm$ 6
B	133 $\pm$ 11	141 $\pm$ 12	135 $\pm$ 3	135 $\pm$ 5	135 $\pm$ 7
Diastolic blood pressure					
W	82 $\pm$ 3	70 $\pm$ 6	77 $\pm$ 2	87 $\pm$ 9	93 $\pm$ 9
B	81 $\pm$ 4	87 $\pm$ 7	77 $\pm$ 1	81 $\pm$ 3	92 $\pm$ 3
Creatinine (mg/dL)					
W	1.4 $\pm$ 0.1	1.4 $\pm$ 0.3 [†]	13.5 $\pm$ 0.8 [†]	11.4 $\pm$ 1.3	3.6 $\pm$ 0.6
B	1.2 $\pm$ 0.1	3.0 $\pm$ 0.5	15.7 $\pm$ 0.6	15.4 $\pm$ 1.3	2.5 $\pm$ 0.7
Blood urea nitrogen (mg/dL)					
W	17 $\pm$ 2	24 $\pm$ 4	92 $\pm$ 5 [†]	80 $\pm$ 13 [†]	70 $\pm$ 21
B	15 $\pm$ 2	38 $\pm$ 6	81 $\pm$ 3	61 $\pm$ 4	37 $\pm$ 11
Protein (g/dL)					
W	6.9 $\pm$ 0.2	5.0 $\pm$ 0.9 [†]	6.3 $\pm$ 0.1 [§]	7.0 $\pm$ 0.4	6.8 $\pm$ 0.3
B	7.1 $\pm$ 0.1	6.8 $\pm$ 0.4	7.0 $\pm$ 0.1	6.7 $\pm$ 0.2	6.9 $\pm$ 0.3
Albumin					
W	4.5 $\pm$ 0.1	2.3 $\pm$ 0.4	3.8 $\pm$ 0.1	4.1 $\pm$ 0.1	4.4 $\pm$ 0.2
B	4.4 $\pm$ 0.1	3.2 $\pm$ 0.3	3.8 $\pm$ 0.1	3.5 $\pm$ 0.1	3.9 $\pm$ 0.2

* NRD = normal renal function, NS = nephrotic range proteinuria, HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis, TR = post renal transplant.

[†] $p < 0.01$.

[‡] $p < 0.1$.

[§] $p < 0.001$.

^{||} $p < 0.05$.

TABLE II. 1988 Lipid Profile for Renal Groups* (Study I)

	NRD	NS	HD	CAPD	TR
Total cholesterol (TC) (mg/dL) (Mean $\pm$ standard error of the mean)					
W	217 $\pm$ 8	316 $\pm$ 96	180 $\pm$ 9	257 $\pm$ 27 [†]	282 $\pm$ 34
B	208 $\pm$ 16	269 $\pm$ 24	163 $\pm$ 6	204 $\pm$ 13	253 $\pm$ 29
(High density lipoprotein-cholesterol (HDL-C) (mg/dL)					
W	41 $\pm$ 5 [†]	47 $\pm$ 7	28 $\pm$ 2 [†]	43 $\pm$ 3	39 $\pm$ 3
B	58 $\pm$ 7	67 $\pm$ 9	39 $\pm$ 2	39 $\pm$ 3	37 $\pm$ 5
TC/HDL-C					
W	5.7 $\pm$ 0.8	6.3 $\pm$ 0.9	7.1 $\pm$ 0.7 [§]	6.0 $\pm$ 0.7	7.2 $\pm$ 0.7
B	4.0 $\pm$ 0.7	4.9 $\pm$ 1.1	4.4 $\pm$ 0.2	5.8 $\pm$ 0.6	7.5 $\pm$ 1.3
Apolipoprotein (Apo) A-I (mg/dL)					
W	96 $\pm$ 7	103 $\pm$ 21	80 $\pm$ 3	110 $\pm$ 5	101 $\pm$ 7
B	112 $\pm$ 8	138 $\pm$ 14	89 $\pm$ 2	100 $\pm$ 4	107 $\pm$ 6
Apo B (mg/dL)					
W	81 $\pm$ 11	127 $\pm$ 37	81 $\pm$ 8 [†]	107 $\pm$ 30	112 $\pm$ 15
B	75 $\pm$ 14	99 $\pm$ 17	63 $\pm$ 2	82 $\pm$ 7	121 $\pm$ 27
A-I/B					
W	1.3 $\pm$ 0.2	.87 $\pm$ 0.1	1.1 $\pm$ 0.1 [†]	1.3 $\pm$ 0.3	0.9 $\pm$ 0.1
B	1.8 $\pm$ 0.4	1.8 $\pm$ 0.4	1.5 $\pm$ 0.1	1.4 $\pm$ 0.1	1.1 $\pm$ 0.2

* NRD = normal renal function, NS = nephrotic range proteinuria, HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis, TR = post renal transplant.

[†] $p < 0.1$.

[‡] $p < 0.01$.

[§] $p < 0.001$.

^{||} $p < 0.05$.

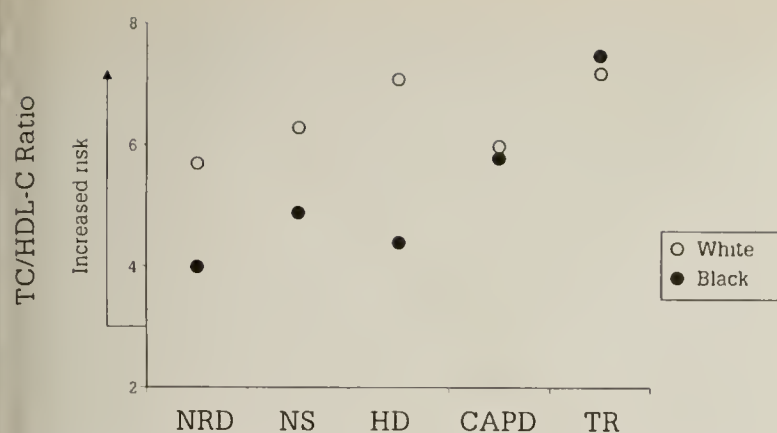


FIGURE 2. Mean total cholesterol (TC)/high density lipoprotein-cholesterol (HDL-C) risk ratio for groups by race (NRD = normal renal function, NS = nephrotic range proteinuria, HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis, TR = post renal transplant).

addition, HD patients had lower TC, TC/HDL-C, apo A-I, and apo B than CAPD patients, and women had higher TC than men.

When lipid profiles were studied longitudinally by yearly intervals, there were no consistent significant changes seen; over two years; apo B fell and A-I/B rose. Race had no significant effect on any of the longitudinal data.

It is well known that in the general population blacks have a favorable lipid profile and, despite increased hypertension, lower cardiovascular mortality. We found that this statement is valid across the spectrum of renal dis-

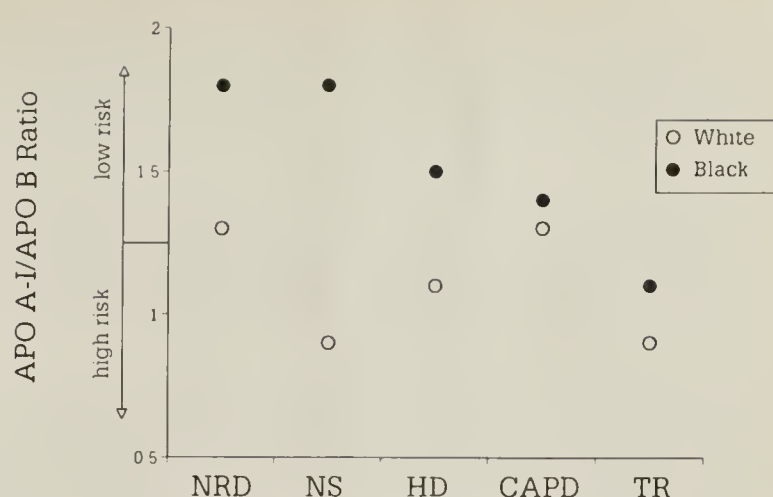


FIGURE 3. Mean apolipoprotein (apo) A-I/apo B anti-atherogenic risk ratio for groups by race (NRD = normal renal function, NS = nephrotic range proteinuria, HD = hemodialysis, CAPD = continuous ambulatory peritoneal dialysis, TR = post renal transplant).

ease. Our results in the ESRD population are compatible with the earlier report of Goldberg et al,¹² and extend their observations further by including diabetics and CAPD patients in this multivariate analysis.

We conclude that race, gender, and dialysis modality all exert significant effects on the lipid profiles of ESRD patients. Also, the effect of race on lipids may explain the reduced incidence of coronary disease and mortality in blacks with ESRD despite their increased incidence of hypertension.

TABLE III. Demographics for an Evolving Cross Section of Patients

	Hemodialysis				Continuous Ambulatory Peritoneal Dialysis			
	1987	1988	1989	1990	1987	1988	1989	1990
N	88	101	136	149	41	25	38	59
Females	47	53	68	73	17	12	17	31
Males	41	48	68	76	24	13	21	28
Whites	24	23	37	41	13	5	9	17
Blacks	51	59	76	82	24	19	25	32
Hispanics	13	19	23	26	4	1	4	10
Non-diabetic	59	68	90	97	29	19	29	46
Diabetic	29	33	46	52	12	6	9	13

TABLE IV. 1989 Lipid Profiles Stratified by Race and Dialysis Modality

	Total Cholesterol (TC) (mg/dL)	High Density Lipoprotein-Cholesterol (mg/dL)	TC/HDL-C	Apolipoprotein (Apo) A-I (mg/dL)	Apo B (mg/dL)	A-I/B
Hemodialysis (mean $\pm$ standard error of mean)						
(all)	169 $\pm$ 4	38 $\pm$ 1	4.9 $\pm$ 0.2	90 $\pm$ 2	66 $\pm$ 2	1.6 $\pm$ 0.1
Whites	161 $\pm$ 8	33 $\pm$ 2	5.5 $\pm$ 0.4	79 $\pm$ 4	66 $\pm$ 5	1.4 $\pm$ 0.2
Blacks	172 $\pm$ 6	41 $\pm$ 2	4.5 $\pm$ 0.2	96 $\pm$ 3	65 $\pm$ 3	1.7 $\pm$ 0.1
Hispanics	171 $\pm$ 9	36 $\pm$ 3	5.3 $\pm$ 0.5	91 $\pm$ 3	67 $\pm$ 4	1.5 $\pm$ 0.1
<i>p</i> *	NS†	<0.02	= 0.05	<0.002	NS	NS
Continuous ambulatory peritoneal dialysis (all)						
(all)	217 $\pm$ 9	45 $\pm$ 5	5.9 $\pm$ 0.5	109 $\pm$ 5	96 $\pm$ 8	1.3 $\pm$ 0.1
Whites	209 $\pm$ 9	33 $\pm$ 3	7.0 $\pm$ 1.2	103 $\pm$ 10	103 $\pm$ 18	1.1 $\pm$ 0.2
Blacks	217 $\pm$ 12	51 $\pm$ 4	5.2 $\pm$ 0.5	111 $\pm$ 6	92 $\pm$ 9	1.3 $\pm$ 0.3
Hispanics	242 $\pm$ 38	—	—	—	—	—
<i>p</i> *	NS	<0.02	NS	NS	NS	NS

* One-way ANOVA by race.

† NS = not significant.

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A retrospective analysis of the metabolic status of stone formers in the New York City metropolitan areas

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ABSTRACT. Eighty stone-forming patients were evaluated as outpatients for risk factors involved in stone formation. Analyses of the major stone risk parameters in the 24-hour collections indicated low volume (<2L) in about 79% of these patients. Forty percent of all patients were found to be hypocitraturic, 30% were hyperoxaluric, 18% were hypercalciuric, and 13% were hyperuricosuric. Sixty-one percent of the patients had a normal calcium load study; of these, four patients were uric acid stone formers. The remaining 39% of patients were classified as either absorptive hypercalciuric (16 patients), or fasting hypercalciuric with normal (12 patients) or elevated (3 patients) serum parathyroid hormone (PTH) levels. Of these 31 patients, 61% were not hypercalciuric on the basis of the 24-hour urine collections.

The protocol provided a diagnosis in over 98% of patients. Low urinary volume was the only defect found in 5% of patients, while more than one risk factor was identified in 93%. (NY State J Med 1991; 91:196-200)

Several reports have appeared in the literature over the last decade regarding the classification of patients who form kidney stones. There have been various approaches to dividing patients into groups depending on the biochemical basis of their disease.¹⁻⁸ Many of the approaches to classifying calcium stone formers involve a combination of blood and urine tests in addition to a calcium load study.^{1,4,8} It is also important to assess the role of dietary correlates in stone formation, since epidemiologic and experimental studies implicate certain dietary factors such as fluid, protein, calcium, oxalate, and others in influencing an individual's risk of stone formation.⁹⁻¹¹ In addition, family, medical, and medication history are also evaluat-

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ed. Since the majority of stones are either calcium oxalate stones (>80%) or mixed calcium stones, the laboratory testing is primarily, but not exclusively, concerned with calcium metabolism. Other major stone components such as oxalate and uric acid are also measured in both urine and blood.

This report presents the results of the metabolic evaluation of 80 stone-forming patients. The basic diagnostic criteria and features of the evaluation protocol employed here have been previously published.^{1,4,8} The protocol provided for a diagnosis in over 98% of patients and, like previous studies performed in various geographic locations, this study also demonstrated that the majority of patients in the New York area have multiple identifiable risk factors for stone formation.

PATIENTS

The data presented here were derived from the metabolic evaluation of 80 adult patients (51 male and 29 female) between 19 and 75 years of age. All patients were referred to the Kidney Stone Center on an outpatient basis. A cross-section of New York's black, Hispanic, and white population is represented in this group of stone formers. Although stone analysis reports were not available in all cases, the majority of these patients were known to be calcium stone formers, and four patients were known uric acid stone formers. The complete metabolic evaluation required two scheduled visits to the center. During the first visit, a physical examination was performed, and information concerning the history of stone recurrence was recorded. The calcium-load study and the analyses of serum and urine specimens are routinely performed at the center according to the protocol described by Drach et al.⁴ Total fluid intake and dietary intake of calcium and protein were quantitated on the basis of the three-day dietary intake record in addition to a food frequency questionnaire. Due to the inherent difficulties in precisely quantitating dietary oxalate intake, it was estimated over a 30-day period using the following ranking. Different foods were assigned points on the basis of whether they had a low-, mid-, or high-range oxalate content. In this way, the daily mean $\pm$ standard deviation (SD) established for dietary oxalate intake of healthy persons was 20.8 ± 6.8 ; individuals consuming > 20 , 15 – 20 , and < 15 points/day were considered to have a high, moderate, and low dietary oxalate content, respectively.

Urinary volume was considered low for stone-forming patients if it was less than 2 liters per 24 hours.⁹ The normal ranges for serum and urinary electrolytes and organic solutes have been established by the hospital laboratories, and these tests were performed as part of a multichannel screen. Urinary citrate was measured using the Boehringer-Mannheim citric acid kit; the test yielded 320 mg/24 hours as the normal lower limit. Urinary cAMP and serum PTH levels were determined by the Instar radioimmunoassay and by the Allegro intact PTH immunoassay system (IRMA), respectively. Serum and urinary oxalate determinations are routinely performed in the authors' laboratory using previously published methodology.^{12,13} The current serum oxalate assay incorporates modifications in sample handling and preparation as suggested by Costello and Landwehr.¹⁴ In our laboratory, serum oxalate was determined to be a mean of $2.54 \pm 0.88 \mu\text{mol/L}$ in 48 healthy individuals, and this agrees well with recently published values.¹⁴ Patients were classified as hyperoxaluric, hypercalciuric, and hyperuricosuric when 24-hour excretion exceeded 40, 300, and 750 mg, respectively. Fasting hypercalciuria was defined by a urinary calcium/creatinine ratio of 0.11, while absorptive hypercalciuria was defined by a ratio of 0.2 after the calcium load.^{1,4} The results obtained from a group of 15 healthy, non-stone forming individuals (8 males, 7 females) who followed the same protocol as the patients permitted comparisons for the purpose of statistical analysis, and these results fell within the normal ranges previously established by the hospi-

tal laboratory for urine and serum chemistries.

Statistical Methods. Statistical analyses of the data obtained from patients and controls were performed using Student's t-test (two-tailed) to establish the significance of the difference between means. A one-way analysis of variance was employed, in conjunction with Duncan's multiple range test, to establish the significance of difference among the means of three or more groups. A correlation between two parameters was determined by way of a simple linear regression analysis. Differences were considered significant at $p \leq 0.05$.

RESULTS

The mean excretion of all substances, with the exception of calcium, oxalate, and citrate, was not significantly different between the group of stone formers and the group ($N=15$) of healthy non-stone forming individuals following the same protocol. The mean 24-hour urinary excretion of calcium and oxalate was significantly higher in the patient group (193 ± 96 mg of calcium, and 32.8 ± 17 mg of oxalate), and citrate excretion was found to be significantly lower in the patient group (398 ± 217 mg/24 hour) when compared to the control group (118 ± 61 , 19.8 ± 6.3 , 582 ± 275 mg/24 hr of calcium, oxalate, and citrate, respectively).

The major risk factors for stone formation identified in the 24-hour urine collections of the 80 patients evaluated are presented in Table I. Low urinary volume was found in the majority of patients (79%) and occurred usually in combination with one or more additional risk factors. Low urinary volume was the only defect found in 5% of cases, and more than one risk factor was identified in 93% of the patients evaluated. The next most common risk factors determined in decreasing order of frequency were hypocitraturia (40%), hyperoxaluria (30%), hypercalciuria (18%), and hyperuricosuria (13%).

No differences were observed in urinary excretion of creatinine (51 ± 54 mg/dL), uric acid (17.6 ± 11.3 mg/dL), oxalate (0.7 ± 0.78 mg/dL), and cAMP ($2.1 \pm 3.1 \mu\text{M}/1$) before and after the calcium load. However, significant increases were observed in urinary excretion of calcium (3.8 ± 5.7 to 8.0 ± 8.7 mg/dL) and magnesium (1.4 ± 1.6 to $2.8 \pm 2.7 \mu\text{M}/L$) following calcium load, and a postprandial decrease in urinary phosphate excretion was observed (25.3 ± 28 to 21.4 ± 26.6 mg/dL). With the exception of urinary magnesium excretion under fasting conditions, which was significantly higher in the control group ($3.6 \pm 0.29 \mu\text{M}/L$), all other mean values were comparable between the patients and the controls. When all of the above data were computed on a temporal basis, ie, excretion in mg/hr, the results did not change. It is also noteworthy that the mean creatinine clearance (which was calculated using urine and serum creatinine values determined under fasting conditions) was not different when the patient group (142 mL/min) was compared to the control group (151 mL/min). Serum oxalate ($5.5 \pm 4 \mu\text{M}/L$) and uric acid (5.7 ± 1.5 mg/dL) concentrations in the patients were found to be significantly higher in the fasting state when compared to the control group, but all other serum parameters were similar. It should be noted, however, that the mean serum uric acid level of the stone formers was within normal limits. Small but significant postprandial increases were observed in serum calcium and phosphorus levels, while serum PTH decreased after the calcium load.

The calcium load study permitted a further breakdown of patients with respect to calcium absorption, excretion, and/or resorption, and these results are shown in Table II. Four of the 49 patients with a normal calcium load study were uric acid stone formers, hence,

TABLE I. Major Stone-Formation Risk Factors Identified in 24-Hour Urine Collections of 80 Stone-Forming Patients

Risk Factor	No. Patients
Low volume	63 (79%)
Hypocitraturia	32 (40%)
Hyperoxaluria	24 (30%)
Hypercalciuria	14 (18%)
Hyperuricosuria	11 (13%)

TABLE II. Grouping of 80 Stone-Forming Patients on the Basis of the Calcium-Load Study

Result	No. Patients
Normal study	49 (61%)*
Absorptive hypercalciuria, normal PTH	16 (20%)
Fasting hypercalciuria, normal PTH	12 (15%)
Fasting hypercalciuria, increased PTH	3 (4%)

* Four patients had uric acid stones.

about 56% of all patients who formed calcium-containing stones had a defect, other than a problem with calcium metabolism. Absorptive hypercalciuria or fasting hypercalciuria with/without an elevated serum PTH was detected in 21% and 20%, respectively, of the 76 patients who formed calcium-containing stones. Of the three patients with fasting hypercalciuria and elevated fasting serum PTH, two patients were classified with suspicion of primary hyperparathyroidism. Both of these patients exhibited elevated fasting serum calcium (11.19 and 10.9 mg/dL) and PTH (>68 pg/mL), in addition to excessive urinary excretion of calcium, phosphate, and magnesium before and after the calcium load study.

The stone forming individuals with normal calcium load study results excreted significantly less calcium on a 24-hour basis (164 ± 89 ; $N = 49$; computed as an average of the total calcium in the two 24-hour collections) when compared to individuals classified with either absorptive hypercalciuria (214 ± 62 ; $N = 16$) or fasting hypercalciuria (241 ± 138 ; $N = 15$). It is of interest to note that 61% of the 31 patients with "abnormal" calcium-load study results were normocalciuric on the basis of their 24-hour urine collections. Curiously, two patients with a normal calcium-load study exhibited hypercalciuria in the 24-hour urine collections—the cause of their hypercalciuria is not immediately apparent.

Hypocitraturia was observed in 40% of patients, and the mean 24-hour excretion in this group was 192 ± 80 mg, which is significantly lower than that observed in the remaining patients (534 ± 164 ; $N = 48$) or the control group (546 ± 190 ; $N = 15$). The 24 stone formers who were classified as hyperoxaluric had a mean 24-hour oxalate excretion of 51 ± 19 mg, and 75% of these patients were also hyperoxalemic (6.88 ± 3.24 $\mu\text{mol/L}$; $N = 18$). Mean urinary oxalate excretion and serum oxalate in the remaining 56 patients were determined to be 24 ± 7.6 mg/24 hours and 2.55 ± 1 $\mu\text{mol/L}$, respectively, which compared well with normal mean values. Sixty-nine calcium stone forming patients had a mean 24-hour urinary uric acid excretion of 396 ± 166 mg/24 hour, which is within the normal range established by our laboratory. Although only 4 of the 80 patients evaluated were uric acid stone formers, 7 patients with calcium stones were classified as hyperuricosuric on the basis of the 24-hour urine collections (937 ± 230 mg/24 hours; $N = 10$ because one patient with uric acid stones was excluded). The latter patient had normal serum and urinary uric acid levels and exhibited a low urine acidity ($\text{pH} = 5$) in addition to hypocitraturia).

Dietary Analyses. The average daily intake of fluid, calcium, oxalate, and protein of the 80 stone-forming patients is presented in Table III. Mean daily fluid intake of the stone-forming group was 1.9 liters, which is about 75% of the minimum recommended fluid

intake to ensure a urinary output of at least 2 liters per day. As shown in Table III, fluid intake ranged widely, with 28% of patients ingesting less than 1.5 liters and 30% ingesting between 1.5 and 2 liters of fluid daily. Only 14% of patients consumed a fluid volume of greater than 2.5 liters.

Also shown in Table III is the mean calcium intake of the patient population, which was similar to the recommended dietary allowance (RDA) of 800 mg/day. (The RDA for both calcium and protein is based on the levels reported in *Recommended Dietary Allowances*, Washington DC, National Academy of Sciences, 1980 edition). While one third of the stone formers consumed 75% or less of the RDA for calcium, 40% of the patients consumed calcium in excess of the RDA.

No significant differences were observed in dietary oxalate intake between healthy controls and either the 56 patients with normal 24-hour oxalate excretion or the hyperoxaluric patients. More than half (54%) of the stone formers consumed a high oxalate diet, while 50% of the controls ingested moderate amounts of oxalate, compared to only 18% of stone formers. Twenty-eight percent of the patients consumed a low oxalate diet, compared with 14% of the controls.

The mean daily protein intake for the 51 male patients evaluated was greater than 60% in excess of the RDA for men (RDA = 56 g/day). Forty-seven of these male patients consumed greater than 100% of the RDA for protein. Of this group of 47 men, 33% consumed between 100% and 150% of the RDA, 37% consumed 150–200% RDA, and 19% consumed in excess of 200% of the RDA for protein. Similarly, mean daily protein consumption by the female patients was also in excess (>50%) of the established RDA for women (RDA = 44 g/day). Among female patients, 89% consumed greater than 100% of the RDA for protein; 46% consumed between 150% and 200% of the RDA for protein and 9% of these patients consumed in excess of 200% of the RDA.

DISCUSSION

Many clinical studies have attempted to identify differences between stone-forming individuals and healthy subjects on the basis of urinary electrolyte and organic solute excretion.^{1–8,15–19} The present study concludes that stone-forming individuals have a significantly higher mean 24-hour excretion of calcium and oxalate and a significantly lower mean excretion of citrate. In addition, serum oxalate concentrations were significantly higher than normal in the stone formers evaluated in this study.

While the importance of maintaining a high urinary volume is generally recognized, most studies do not present data regarding the percentage of patients with inadequate volume excretion. In the present study, a high percentage (79%) of patients did not excrete a minimum urine volume of 2 liters to ensure an adequate dilution effect on the excretion of stone-forming salts.⁹ This observation alone underscores the importance of patient education in maintaining a high fluid intake.

In previous studies, hypocitraturia was reported to occur in up to 55% of stone formers,^{8,17} and it was the most frequent biochemical finding in the present study. It was also evident here that sex differences do exist in urinary citrate excretion among healthy individuals. A higher 24-hour excretion of citrate was observed in females (mean = 582 for females and mean = 512 for males), and this sex difference disappeared within the stone-forming group (mean = 397 for females and mean = 405 for males).

Hyperoxaluria was found in 30% of these patients, which is somewhat more frequent than previous reports of 12–21% among stone formers with this major risk factor.^{3,4,7,8} In contrast to our finding of a higher serum oxalate, Schwille et al²⁰ reported lower serum oxalate levels in

TABLE III. Fluid, Calcium, Oxalate, and Protein Intake of 80 Stone-Forming Patients (51 Male, 29 Female)

Intake	Mean Standard Deviation	Minimum	Maximum
Fluid (mL/day)	1896 ± 716	600	4400
Calcium (mg/day)	782 ± 346	271	1854
Oxalate (points/day)	20.8 ± 6.8	14.5	37.9
Protein (g/day)			
male	92 ± 29	36	179
female	68 ± 21	30	115

idiopathic calcium stone formers when they were compared to sex-matched controls. In their study, the patients were grouped on the basis of urinary calcium excretion and not urinary oxalate excretion, as in this study. Grouping our patients according to the type of calciuria did not change the result, hence the reason for this contrast in results is unclear. However, the finding by Schwille et al of no difference in fasting urinary oxalate excretion between patients and controls is consistent with our result. An elevation in postprandial urinary oxalate was observed in another study by Schwille et al²¹ in patients with absorptive and renal leak calciuria when they ingested a calcium meal similar to that consumed by our patients. In sharp contrast, stone formers in the present study who exhibited absorptive and renal leak calciuria had decreased postprandial urinary oxalate excretion (mean = 0.99 to mean = 0.74 mg/hr, N = 16; mean = 1.82 to mean = 0.85 mg/hr, N = 15, before and after, respectively). A predictable decrease in urinary oxalate excretion can occur if excess intraluminal calcium is available to bind with oxalate. In fact, Schwille et al²¹ reported a decrease in intestinal ¹⁴C tracer oxalate absorption during a 24-hour evaluation period following the test calcium meal, but these authors could not reconcile this result with the increase in postprandial oxalate excretion.

The classification of hypercalciuria on the basis of the 24-hour urine collection was determined in 18% of our patient population. Further evaluation of how each patient responded to an oral calcium challenge revealed a diagnosis of either absorptive or renal leak calciuria in more than 40% of the 76 patients who formed calcium stones. This higher percentage is more consistent with the incidence of hypercalciuria found in other studies^{4,8} and underscores the importance of including a calcium-load study in the metabolic evaluation of patients who form calcium stones. Currently, a calcium-load study is not included in the protocol for patients identified, in advance, to have pure uric acid stones. The present study identified a somewhat higher number (21%) of patients with absorptive hypercalciuria, compared with renal leak calciuria (16%), and resorptive hypercalciuria was identified in 3 (4%) patients. Other studies disagree on the incidence of absorptive versus renal leak calciuria.^{1,4,5,8} Preminger⁸ reports that individuals with absorptive hypercalciuria outnumber those with renal leak by 5:1, while Rous⁵ finds the opposite, with renal leak patients outnumbering those with absorptive hypercalciuria by 3:1.⁵ Most studies do agree, however, that the majority of hypercalciuric patients may be classified as absorptive hypercalciuric.^{1,4,8}

The role of urinary uric acid in calcium stone disease is unclear but reports clearly show that the frequency of hyperuricosuria varies widely among patients evaluated for this risk factor.^{1-4,8,18} A high protein diet has been reported to increase urinary excretion of uric acid,^{10,19} but we found no correlation between protein intake and uric acid excretion when all 80 patients were considered, which agrees with the findings of Griffith et al.¹¹ There was a positive correlation ($r = 0.85$) between these two parameters only in those patients who were both hyperuricosuric and hyperuricemic in the fasting state. Although Coe et al¹⁸ reported that most hyperuricosuric calcium stone formers are normouricemic, we found 5 (45%) of 11 pa-

tients with hyperuricemia. Since dietary protein intake was strongly correlated with uric acid excretion in these patients, perhaps the hyperuricemia resulted from increased uric acid production during the course of endogenous purine metabolism.

Magnesium and phosphate have been identified as inhibitors of calcium stone formation,¹⁹ but the relative importance of the urinary concentrations of these ions is not clear. Lower phosphate excretion by stone formers was reported by Elliot,¹⁵ however, like most investigators,^{3,17} we could not detect any difference in urinary phosphate excretion between stone formers and healthy controls. There are contrary reports in the literature regarding urinary magnesium concentrations in stone-forming patients. Our results revealed that there was no difference between patients and controls in urinary magnesium excretion on a random diet (24-hour collection); yet, under fasting conditions, magnesium excretion was significantly lower in the stone-forming patients. The ingestion of magnesium appears to determine urinary magnesium excretion in this group of stone formers.

Dietary Aspects. Numerous dietary factors have been implicated in contributing to urinary tract stone disease, and we routinely evaluate patients' diets with respect to fluids, calcium, oxalate, and protein. It is important to note here that this was not a pre-designed study, and the controls were not matched for sex, age, or socioeconomic background; hence, interpretations of the results are limited. These data were examined retrospectively for the purpose of this report, and several aspects are noteworthy.

The finding that about 20% of stone formers had a urinary volume of 2 liters or more is consistent with the parallel finding that only 14% of the patients drank fluids in excess of the 2.5 liters required for this level of volume excretion. Low urinary volume was the only finding in 5% of the 80 patients, and this was a direct result of low fluid intake by these individuals. This study revealed that more than 40% of the patients consumed calcium in excess of the RDA, and there was a wide range in calcium intake among the patients. No correlation was evident between calcium intake and calcium excretion in any subgroup of the patient population, which agrees with previous results.¹⁰ Robertson¹⁰ observed that stone formers ingest more oxalate than healthy controls, but he judged that the difference was too small to account for the observed hyperoxaluria in his patient group. In addition, Robertson found no correlation between oxalate intake and urinary oxalate excretion in these patients.¹⁰ We were able to confirm that oxalate excretion did not correlate with oxalate intake in either the control group or the stone formers. Oxalate intake by the healthy controls included in this study ranged between 435 and 1,139 points/day, and most of these individuals (64%) consumed a low to moderate oxalate diet, compared to most (54%) of the stone formers who consumed a high oxalate diet. Epidemiologic studies have shown that there is a strong correlation between increased consumption of animal protein and stone disease. While protein intake in the patient group evaluated here appears to be high, it is comparable with the average daily protein intake by individuals living in the United States.

Finally, it was interesting to note an increased incidence of hypercholesterolemia among this patient group when

compared to the general US adult population. Seventy-nine percent of patients had total serum cholesterol levels that fell into the borderline high and high category—200–239 and >240 mg/dL, respectively, compared with 57% of adult Americans.²² The hypercholesterolemia observed in these patients may be indicative of a greater consumption of high cholesterol foods such as meat. Perhaps this can be considered as indirect support of the notion that a diet high in animal protein contributes to stone disease.

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Identification of asymptomatic renal cell carcinomas utilizing modern radiographic techniques

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ABSTRACT. The more liberal use of ultrasonography and computed tomography has made more common the incidental discovery of renal masses.

The charts of 105 patients surgically treated for renal cell carcinoma at a teaching hospital from 1983 to 1987 were reviewed. The incidence of incidentally found asymptomatic tumors was 47% (49/105 patients). Of the incidentally found tumors, 55% were stage I and only 14% were stage III; for symptomatic patients, 39% of tumors were stage I and 27% were stage III. This study also found that the classical triad of pain, hematuria, and flank mass was present in only 3.8% (4/105) of patients. Tumors found incidentally will usually be of lower pathologic stage and may carry a better prognosis. (NY State J Med 1991; 91:200–202)

Historically, the diagnosis of renal cell carcinoma has re-

lied on studies performed after the onset of symptoms, including pain, gross hematuria, and palpable flank mass, which herald both localized and widespread metastatic disease. However, increasing use of computed tomography, ultrasonography, and arteriography has greatly increased the number of incidentally diagnosed renal carcinomas. Early diagnosis and prompt, appropriate surgical extirpation, as well as other factors, including lack of perirenal fat invasion by tumor, may favorably affect the overall prognosis.¹ This review was undertaken to determine the incidence of renal cell carcinoma diagnosed in asymptomatic patients, and to compare the pathologic stage of these tumors to those that are suspected at the time of diagnosis, in an attempt to determine whether those tumors found incidentally are of lower stage.

PATIENTS AND METHODS

The records of 105 of 115 consecutive patients with renal cell carcinoma treated surgically at a teaching hospital from 1983 to 1987 were reviewed. The presenting signs and symptoms of 105 patients with 106 tumors were evaluated. Four patients with oncocyctomas were excluded from this review. The radiographic

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TABLE I. Robson Modification of the Flocks and Kadesky Staging System of Renal Cell Carcinoma

Stage	Description
I	Tumor confined to renal parenchyma
II	Tumor invading through renal capsule with Gerota's fascia intact
IIIA	Renal vein or inferior vena cava grossly involved
IIIB	Lymphatic involvement
IVA	Tumor involving adjacent organs
IVB	Distant metastases

studies that ultimately led to the diagnosis of renal cell carcinoma were determined in each case. The cases were designated as incidental or non-incidental, based on whether a urologic malignancy was suspected and sought at the time of the study. The diagnosis of renal cell carcinoma was made incidentally by one of the following methods: plain film of the abdomen, including the kidney, ureter, and bladder (KUB); barium enema; sonography; abdominal-peripheral arteriography; intravenous pyelography (IVP); or abdominal and spinal computed tomography (CT). The various complaints being evaluated included diverticulitis, peripheral vascular disease, gynecologic disease, spinal stenosis, and cholelithiasis. A number of incidentally found renal cell carcinomas were diagnosed based on studies for other urologic diseases, including routine pre-prostatectomy evaluations, evaluation of recurrent urinary tract infections and hematospermia, and retrograde pyelography for the evaluation of transitional cell carcinoma of the bladder. Cases were considered non-incidental (symptomatic) if the tumor was discovered on IVP, ultrasound, or CT as part of an evaluation of hematuria, flank pain, flank or abdominal mass, or suspected metastatic disease. Admission histories and physical examinations were reviewed, as were admission urinalyses to determine the presence or absence of the classic triad of pain, flank mass, and hematuria.

Tumor stage was determined in all cases by reviewing the pathology reports and tumor registry data. Only patients with histologically diagnosed renal cell carcinoma were included in this study. As previously mentioned, the four patients with oncocytomas were excluded. The Robson modification of the staging system proposed by Flocks and Hodesky was utilized in all cases (Table I).² Statistical analysis of all data was performed using the chi-squared test.

RESULTS

A total of 116 nephrectomies were performed on 115 patients (one patient had bilateral tumors) between 1983 and 1987 for renal cell

carcinoma. Four patients with oncocytomas were excluded from the study. One hundred and five charts were available for review—77 men (73%) and 28 women (27%). Among those with incidentally diagnosed disease, 36 were men (73%) and 13 were women (27%).

Of the 105 patients included in the study, 49 (47%) underwent radical nephrectomy for renal cell carcinoma that was found incidentally on various imaging studies. Table II presents the diagnostic studies by which these incidental tumors were found. Eighteen renal cell carcinomas were found in 17 patients by computed tomography (37% of the incidentally diagnosed tumors). Fourteen incidental renal cell carcinomas were detected on IVP (29%); nine of these tests were performed as routine components of upper tract work-ups prior to transurethral prostatectomy. Ultrasonography diagnosed ten unsuspected renal cell carcinomas (20%). Five incidental renal cell carcinomas were found on abdominal-peripheral arteriography for various symptoms of peripheral vascular disease.

Table III shows the tumor stages of all patients reviewed. Of the 49 with incidental diagnoses, 27 (55%) were stage I, and only seven (14%) were stage III. The non-incidental group had 56 patients, of which 22 (39%) were stage I and 15 (27%) were stage III. Of the two cases of non-incidental stage IV renal cell carcinoma, both were accurately staged prior to surgery, but nephrectomy was performed in one for bleeding and in the second to obtain tissue to enter the patient in an immunotherapy protocol. These data are statistically significant ($p < 0.01$), confirming the hypothesis that incidentally found renal cell carcinomas are of lower stage than those that are suspected at the time of diagnosis.

The frequency of the classical findings of pain, palpable flank mass, and hematuria in these patients was also examined. Overall, only 4 of 105 (3.8%) patients presented with this triad of symptoms. Their tumor stages were II (one patient), III (two patients), and IV (one patient).

Forty-four of 106 (42%) tumors were on the right side, and 62 of 106 (58%) were on the left side. Of the incidentally found tumors, 37% were right-sided, while 46% of non-incidentally found tumors were right-sided. These data are not statistically significant, indicating that incidental tumors are not more likely to occur on either side than are non-incidental renal cell tumors.

DISCUSSION

Since Grawitz³ described renal cell adenocarcinoma in 1883, there have been many large series focused on its diagnosis. Far fewer series have been reported since the routine use of computed tomography and ultrasonography. For many years, the diagnosis was made only when the classical triad of renal cell carcinoma, flank pain, gross hematuria, and a palpable abdominal mass were

TABLE II. Incidentally Diagnosed Renal Cell Carcinomas According to Radiographic Study Utilized

Reason for Study	Intravenous Pyelography	Ultrasonography	Computed Tomography	Arteriography	Barium Enema	Other
Bladder tumor	—	—	—	—	—	1*
Benign prostatic hypertrophy	9	3	—	—	—	—
Dysuria	2	—	—	—	—	—
Hematospermia	1	—	—	—	—	—
Colic	1	—	—	—	—	—
Anemia	—	—	2	—	—	—
Spinal disease	—	—	2	—	—	—
Vague abdominal complaints	—	2	6	—	—	—
Specific gastrointestinal complaints	—	—	5	—	2	—
Gynecologic complaints	1	2	—	—	—	—
Metastatic evaluation	—	—	2	—	—	—
Peripheral vascular disease	—	—	—	5	—	—
Gallbladder disease	—	3	—	—	—	—
Total	14	10	17	5	2	1

* Retrograde pyelography.

TABLE III. Pathologic Staging of 105 Resected Renal Cell Carcinomas

Pathologic Stage	Incidental	Non-incidental
I	27 (55%)	22 (39%)
II	14 (29%)	17 (30%)
III	7 (14%)	15 (27%)
IV	1 (2%)	2 (4%)
Total	49 (100%)	56 (100%)

present.⁴ Only 3.8% of the patients described here presented with this classic triad, which is less than the 5–15% reported throughout the literature even before the advent of CT and ultrasound.^{4–7} Many more patients presented historically with the non-urologic symptoms of weight loss, fatigue, and generalized malaise, all manifestations of advanced carcinoma.

Prior to the era of CT, studies described incidental findings of renal cell carcinoma in up to 20% of cases, but these included IVPs for evaluation of microhematuria, which we included in the non-incidental group.⁴ Konnak et al⁸ reported that 48% of the renal cell carcinomas in their study were discovered incidentally, a figure which compares favorably with our findings of 47%.⁸ Rittenhouse and Hadley⁹ reported incidental findings in 30% of the cases, but their data indicated that this figure had not changed with the more liberal use of CT and ultrasound. This claim was refuted by the former group, which described only 13% of cases discovered incidentally in the earlier arm of their study, which dated back to the pre-CT era.⁸ Also in the pre-CT era, Skinner et al⁵ noted that 7% of their patients with renal cell carcinoma were found incidentally during the course of another operation, a diagnostic method that has not been described in any recent studies. Today, these tumors would no doubt be found preoperatively on CT evaluation of the primary problem.

In the study presented here, the tumor stage of those renal cell carcinomas found incidentally was lower than those that presented with accompanying symptoms ($p <$

0.01). Thompson and Peek,¹⁰ in their recent study, found a significantly increased survival in those patients whose tumors were found incidentally. Thus, the increased use of modern radiographic imaging techniques has facilitated the identification of asymptomatic renal cell carcinoma. This may significantly improve overall patient survival statistics, though Golimbu et al¹ have shown that lower tumor stage alone does not necessarily portend a better prognosis. Evidence of perirenal fat invasion was associated with lower five- and ten-year survival rates, while various other tumor characteristics, including tumor size less than 5 centimeters in diameter, were associated with a better prognosis.¹ Furthermore, those tumors that are being identified earlier may be more amenable to renal conservation surgery than are those tumors identified later.

In conclusion, the incidental finding of renal cell carcinoma by computed tomography, ultrasonography, and other modern radiographic imaging techniques has become increasingly more common as these techniques are used in the evaluation of other symptoms and disease states. These incidentally found tumors are of lower stage than non-incidentally found renal cell tumors. The increasing use of magnetic resonance imaging may further increase the number of incidentally found renal cell carcinomas.

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Diabetic nephropathy in the inner city

ELI A. FRIEDMAN, MD

Among inner city blacks in New York City, diabetes mellitus is an endemic disorder of high prevalence. The inner city is defined as several intensely populated urban regions in which blacks and Hispanics comprise the majority of the population, and poverty is pervasive. Although few studies detail the natural history of diabetic nephropathy in blacks, race is a major variable contributing to both the risk of development and the course of diabetic nephropathy.¹ Racial variation in the prevalence of diabetes has been repeatedly reported.² For example, more than three of four adult Indians in Nauru, Malaya, and over half of the Pima Indians in the United States develop clinical diabetes. The toll in reduced life expectancy in Nauru is severe (39.5 years for men and 48.5 years for women) because of the complications of diabetes.³ Similarly, Pima Indians face an inordinately high probability of renal failure due to diabetic nephropathy.²

Throughout the 50 states, blacks have a greater prevalence of diabetes and its complications than do whites; like blacks, Hispanics—especially Mexican-Americans—have a threefold greater prevalence of diabetes than do non-Hispanic whites.⁴

That race is a leading determinant is evident from epidemiologic studies in Alaska. Age-adjusted prevalence rates for diabetes by ethnic group were 27.2/1,000 among Aleuts, 22.0/1,000 among Alaskan Indians, and 8.8/1,000 among Alaskan Eskimos.⁵ Similar racial differences in diabetes prevalence are reported in West Indian blacks who have a prevalence of known diabetes (2.2%) that is double that of the indigenous white population (1.2%).⁶ The extraordinary rise in prevalence of diabetes in the Pimas and other inbred populations has been blamed on fast food, alcoholism, and a high fat diet, all factors operative in the inner city.² Ringrose and Zimmet⁷ theorize that obesity and a high carbohydrate, low fat, Westernized diet and life style, coupled with a formerly underappreciated genetic predisposition, are responsible for the inordinate rate of diabetes in Nauru.⁷ Other Asian populations also evince wide variations in the prevalence of diabetes, even where diet and life style are less affected by Western influence. In Malaysia, for example, Mustaffa⁸ found an "estimated prevalence" of diabetes much

greater in Indians than in Chinese.

GENETICS AND INNER CITY DIABETES

As is true for Hispanics and American Indians, diabetic blacks have non-insulin-dependent diabetes (NIDDM, Type II) in more than 92% of instances. It is (verbally) reported that of 1.4 million American Indians known to the US Indian Service, there is presently not one case of insulin-dependent diabetes mellitus (IDDM, Type I). IDDM is also rare in Asians. The genetics of diabetes risk and expression are incompletely understood. Furthermore, freedom of travel and emigration has resulted in blurring of formerly pure racial lines. Illustrating this point is a report of testing in American Pima and Papago Indians for the Gm haplotype (Gm3; 5,13,14) by Knowler et al.⁹ This haplotype is thought to assess the extent of Caucasian admixture and was found to be inversely associated with the prevalence of NIDDM.⁹ Indeed, in Pimas, absence of the Gm3; 5,13,14 haplotype translates into a risk factor for diabetes. Genetic admixture, therefore, lessens the reliability of inferences drawn from measurements of diabetes incidence and prevalence by superficial judgment of race.

FAMILIAL VARIABLES IN DIABETIC NEPHROPATHY

In addition to racial differences in the rate of diabetes and nephropathy, certain families at high risk for diabetes have been identified. Seaquist et al.¹⁰ found that the diabetic siblings of probands with diabetic nephropathy who had received a kidney transplant had a higher frequency of nephropathy than did diabetic siblings of diabetic patients without evidence of nephropathy. Familial studies at the Joslin Clinic in Boston suggest an association of genetic predisposition to diabetic nephropathy with a genetic risk for hypertension.¹¹ Recently, it has been noted that parents of children with IDDM and proteinuria have a higher blood pressure than do parents of individuals with IDDM without proteinuria.¹² Measurements of the rate of erythrocyte lithium-sodium countertransport, a marker for the risk of essential hypertension, are increased in diabetic patients with microalbuminuria,¹³ a finding suggestive of broad genetic differences between those diabetic individuals who will and will not develop nephropathy.

Blacks in the inner city have higher incidence rates of hypertension as well as diabetes. In one theory, Tollins and Raij¹⁴ speculate that those diabetic patients who are likely to develop nephropathy have a genetic predisposi-

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tion to hypertension coupled with defective regulation of preglomerular resistance vessels. Following this logic, slight increases in systemic blood pressure may be directly transmitted to glomeruli that have undergone hemodynamic injury. Furthermore, Viberti¹⁵ theorizes that the natural history of diabetes must incorporate consideration of the role of genetic variables, which may accelerate or mute the course of nephropathy in diabetic individuals. In Viberti's view, the subset of those with diabetes likely to manifest diabetic nephropathy have a high level of sodium-lithium countertransport activity (relating closely to the physiologic sodium-hydrogen antiport) in erythrocytes amounting to about 0.55 mmol/L of red blood cells/hour. An inherited predisposition to supranormal sodium-hydrogen countertransport may, in this light, be associated with an increased intracellular pH leading to cellular hypertrophy and hyperplasia.

CONSULTATIONS FOR DIABETIC NEPHROPATHY

The State University of New York (SUNY) Health Science Center at Brooklyn proffers renal care to a large, municipal hospital (Kings County Hospital Center) that cares for indigent, mainly black patients, and a state university hospital (University Hospital of Brooklyn) that cares for a mixture of patients including white, middle class individuals. We reviewed a total of 1,979 renal consultations and admissions completed between January 1, 1987, and December 31, 1989. The large majority of these admissions and consultations, 1,533 (77.5%), were for black patients, while 271 (13.7%) were for whites and 155 (7.8%) were for Hispanic patients (Table I). The number of Asian patients (a total of 13, of whom 3 had diabetes) was too low to allow accurate statistical analysis.

In general, the severity of renal disease is judged by the level of nitrogenous wastes in plasma. An above normal serum creatinine concentration does not occur until at least 70% of renal function has been lost. It follows that the level of serum creatinine in newly evaluated patients serves as a marker for when in the course of renal malfunction consultation was obtained. Among the renal consultation patients seen at SUNY Health Science Center at Brooklyn, the mean serum creatinine concentration was significantly higher ($p < 0.001$) in black patients (8.9 ± 6.3 mg/dL) than in white patients (6.3 ± 4.0 mg/dL). When analyzed separately by gender, black women with diabetes had a higher mean serum creatinine than did white women with diabetes ($p < 0.0001$), and the same relationship held for black men versus white men ($p < 0.01$, Table I). The relatively high serum creatinine concentration in all groups of patients in Table I bespeaks late disease; this creates an atmosphere of urgency with reduced time for thought and planning.

About one in five renal consultations was requested for a diabetic patient. Racial differences were quite evident in mean serum creatinine concentrations. The 308 diabetic blacks were older (mean age 60.1 ± 13.5 years) than the 69 diabetic whites (mean age 51.6 ± 13.4 years), and the mean serum creatinine concentration in diabetic blacks (7.8 ± 4.2 mg/dL) was significantly higher than in whites (5.5 ± 3.8 mg/dL), $p < 0.01$. Black diabetic men had higher serum creatinine levels than did white diabetic men; the same was true for women. The relatively small

TABLE I. Renal Consultations, 1987-1989, University Hospital and Kings County Hospital, By Race, Gender, Diabetes

Group	N	Mean Age (years) $\pm$ Standard Deviation (Range)	Mean BUN* (mg/dL) $\pm$ Standard Deviation (Range)	Mean Creatinine (mg/dL) $\pm$ Standard Deviation (Range)
White	271	56.7 $\pm$ 18.3 (20.0-101.1)	69.2 $\pm$ 37.5 (5-250)	6.3 $\pm$ 4.0 (0.9-20.4)
Black	1,533	51.5 $\pm$ 19.0 (17.2-101.1)	77.1 $\pm$ 43.6 (3-333)	8.9 $\pm$ 6.3 (0.1-40.4)
Hispanic	155	46.9 $\pm$ 16.4 (20.2-89.8)	66.1 $\pm$ 40.2 (5-231)	6.5 $\pm$ 4.5 (0.5-21.5)
All	1,979	51.9 $\pm$ 16.8 (17.2-101.1)	75.0 $\pm$ 42.7 (3-333)	8.4 $\pm$ 6.0 (0.1-40.4)
Diabetic Patients				
All	413	58.2 $\pm$ 14.0 (21.9-91.9)	71.7 $\pm$ 32.0 (9-188)	7.3 $\pm$ 4.1 (0.7-30.9)
Men	155	56.9 $\pm$ 14.7 (24.8-89.8)	75.6 $\pm$ 33.7 (9-188)	7.9 $\pm$ 21.0 (1.0-30.9)
Women	258	58.8 $\pm$ 13.5 (21.7-91.9)	69.3 $\pm$ 30.8 (12-171)	6.9 $\pm$ 14.3 (0.7-23.0)
White	69	51.6 $\pm$ 13.4 (25.9-74.1)	71.4 $\pm$ 34.3 (13-158)	5.5 $\pm$ 3.8 (0.9-14.3)
Black	308	60.1 $\pm$ 13.5 (21.7-91.9)	72.3 $\pm$ 31.3 (9-188)	7.8 $\pm$ 4.2 (0.7-30.9)
Hispanic	32	52.9 $\pm$ 15.8 (29.8-82.5)	70.0 $\pm$ 35.5 (18-153)	6.5 $\pm$ 3.8 (1.0-16.9)
White women	45	47.3 $\pm$ 11.2 (30.1-69.9)	66.8 $\pm$ 30.1 (20-158)	4.9 $\pm$ 2.9 (0.9-11.5)
Black women	204	61.81 $\pm$ 12.3 (21.7-91.9)	69.8 $\pm$ 30.7 (12-171)	7.3 $\pm$ 3.9 (0.7-23)
Hispanic women	9	50.0 $\pm$ 16.9 (31.6-82.5)	70.3 $\pm$ 39.5 (32-134)	7.7 $\pm$ 2.2 (4.6-11.0)
White men	24	59.6 $\pm$ 13.6 (25.9-74.1)	80.0 $\pm$ 40.2 (13-156)	6.5 $\pm$ 3.5 (1.1-14.3)
Black men	104	56.8 $\pm$ 14.9 (24.8-89.8)	77.1 $\pm$ 31.8 (9-188)	8.8 $\pm$ 4.7 (1.7-30.9)
Hispanic men	23	54.1 $\pm$ 15.7 (29.8-81.5)	69.9 $\pm$ 34.8 (18-153)	6.0 $\pm$ 4.2 (1.0-16.9)

* BUN = blood urea nitrogen.

number of diabetic Hispanics (N=32) had a serum creatinine concentration of 6.5 ± 3.8 mg/dL, which fell midway between the mean values for blacks and whites and was not statistically different from either. No explanation for the higher creatinine value in diabetic blacks over whites is immediately evident.

END STAGE RENAL DISEASE (ESRD)

Not surprisingly, the higher incidence of diabetes in blacks carries over into a relatively higher incidence of ESRD attributed to diabetic nephropathy. Blacks have a higher incidence (2.6-fold higher than whites) of "diabetic end-stage renal disease," even when adjusted for the higher prevalence of diabetes among blacks.¹⁶ In an intensively analyzed group of blacks in Michigan, it was found that most individuals with diabetes and ESRD had NIDDM (77%), whereas most white patients with diabetes and ESRD had IDDM (58%) ($p \leq 0.0005$ for the dif-

ference between races). Diabetes type appeared to influence the risk of ultimately contracting ESRD in Michigan over ten years of observation; more individuals with IDDM (5.8%) than NIDDM (0.5%) became uremic. A contrary report, by Ordonez and Hiatt,¹⁷ noted that among NIDDM patients who developed ESRD, once proteinuria occurred, nephropathy progressed at the same rate as is observed in IDDM. Consistent with this view is the population-based study by Humphrey et al¹⁸ of the rate of developing renal failure in a cohort of 2,022 diabetic residents of Rochester, Minnesota. Once proteinuria became persistent in NIDDM, the cumulative risk for chronic renal failure ten years later was 11%. In the Rochester population, made up predominantly of non-Hispanic whites, the cumulative incidence of chronic renal failure was similar for IDDM and NIDDM. As is true for inner city blacks, the cohort with NIDDM was 13.5 times larger than that with IDDM, thereby producing 8.3 times more cases of ESRD than in the cohort with IDDM.

Whether in the inner city, the Pima reservation, or throughout America, the majority of new ESRD patients who have diabetes have NIDDM. Humphrey et al¹⁸ make the important point that estimates of rates of diabetic nephropathy must be population based and not limited to inferences from atypical groups, such as referrals to a specific clinic. Thus, the actual rate of ESRD in diabetes by diabetes type and race remains essentially a guess. No prospective population-based studies of the rate of development of nephropathy in diabetes among Hispanics or blacks have been reported. What is not disputed, however, is that Hispanics and American Indians, both races with an increased incidence of diabetes, also have a greater rate of ESRD. In the United States, Mexican-Americans are the second largest minority group after blacks (comprising 8.8 million in 1980). Like blacks, Hispanics in the United States are concentrated in the inner cities. Hispanics in surveys of southern inner cities have a threefold greater prevalence of renal failure due to NIDDM than do non-Hispanic whites.^{19,20}

INNER CITY MAINTENANCE HEMODIALYSIS

The majority of new ESRD patients seen by our service are inner city blacks. To assess the fate of the subset of individuals who are diabetic, Lowder et al²¹ surveyed 13 hemodialysis units in Brooklyn in 1986 to ascertain demographics, degree of rehabilitation, and diabetes type in diabetic hemodialysis patients. Classification of patients by diabetes type was possible for the majority. Only 31 (13.4%) of 232 diabetic dialysis patients had IDDM, while 177 (76%) had NIDDM. There were 24 (10.3%) patients who could not be classified as to diabetes type. Most (138/232, 60%) diabetic patients were black, and of these, only 15 (10.8%) had IDDM. As shown in Figures 1 and 2, derived from the study by Lowder et al,²¹ it is evident that the 138 black dialysis patients with diabetes were approximately equivalent to the 59 white hemodialysis patients with diabetes in age distribution and duration of diabetes prior to starting maintenance hemodialysis. As shown in Figure 3, however, the majority of black diabetic hemodialysis patients were women (87/138, 63%), whereas the majority of white diabetic hemodialysis patients were men (35/59, 59.3%).

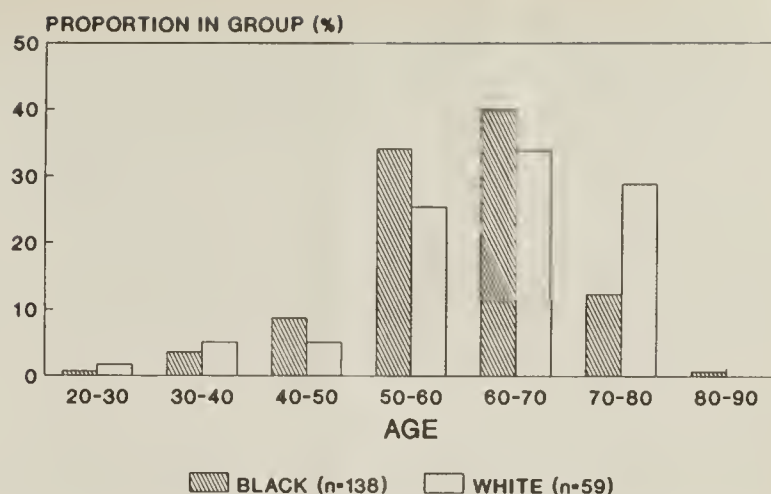


FIGURE 1. Age and race of diabetic individuals undergoing maintenance hemodialysis at 13 dialysis facilities in Brooklyn (N = 197) (data courtesy of Lowder et al²¹).

The therapeutic tragedy of ESRD due to diabetes in the inner city is the slim probability of gaining rehabilitation. From individualized assessment of the Brooklyn population of hemodialysis patients with diabetes it is inferred that rehabilitation was minimal, as indicated by a mean Karnofsky score of only 64.9. (Functional performance of usual activities requires a Karnofsky score above 75.²²) Lowder et al²¹ found that black (64.2), white (66.9), and Hispanic (64.0) diabetic dialysis patients had equally low Karnofsky scores (Fig 4).

There is some unanticipated and encouraging news about diabetes and ESRD in inner city blacks. In all studies to date, black diabetic patients undergoing maintenance hemodialysis have statistically superior survival when compared with white diabetic patients. For example, in an analysis of patient mortality from 1979 to 1985 performed by Dr Philip J. Held at the Urban Institute and reported to the Health Care Finance Administration, racial differences in survival were evident by means of the Cox proportional hazards technique; the probability of dying for diabetic patients subgrouped by age and race was compared to a reference standard group comprised of nondiabetic white patients who carried the diagnosis of chronic glomerulonephritis and were undergoing in-center hemodialysis. White diabetic patients risked death at a rate ranging from 1.54 times (in those less than 45 years old, $p < 0.01$) to 2.20 times (in those older than 60 years, $p < 0.01$), the rate of white nondiabetic patients with glomerulonephritis. Black diabetic hemodialysis patients younger than 60 years, by contrast, were at no increased risk of dying compared to the reference group of white patients with renal failure secondary to glomerulonephritis ($p = 0.19$ to 0.35). We have no explanation for this finding. There were too few concurrent peritoneal dialysis patients in the study population to permit inferences on survival of those utilizing this therapy by race and type of diabetes.

RENAL TRANSPLANTATION IN THE INNER CITY

Blacks are less likely to donate cadaver organs and are less likely to receive a cadaver renal transplant than are whites. Race, in some but not all studies, has been implicated in both patient and graft survival after renal transplantation. Although diabetic recipients have been includ-

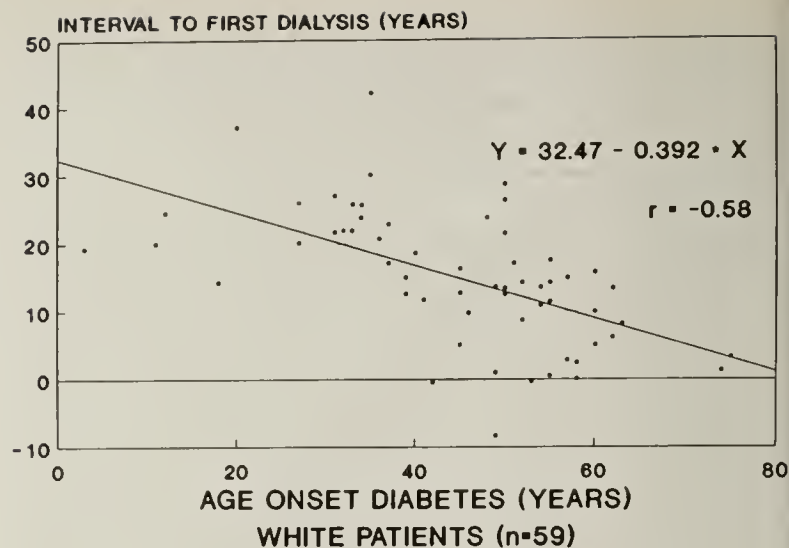
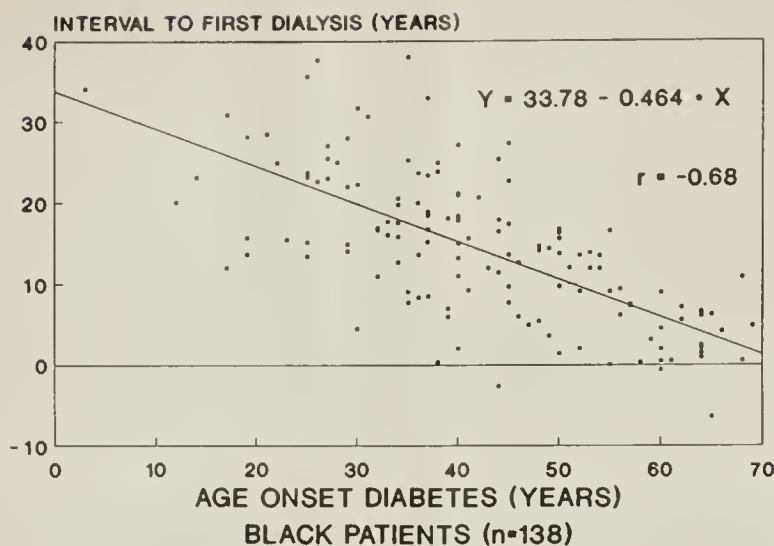


FIGURE 2. Duration of diabetes prior to first hemodialysis by race (data courtesy of Lowder et al²¹). Left, black diabetic patients; Right, white diabetic patients. A shorter interval in blacks is confirmed by the slope of the curves.

ed in studies that purport to show race-determined outcome of a transplant, proportional hazards analysis using diabetes as a variable to determine the effect of race has not been reported. One serious concern raised by Barger et al²³ is that both white and black renal allograft recipients of kidneys donated by blacks have reduced functional graft survival when compared to recipients of kidneys donated by whites. Sustaining this view is the recent report by Dunn et al²⁴ of an analysis of outcome in 666 renal transplant recipients that included 420 whites, 148 blacks, and 98 Hispanics. Although patient survival at five years was similar for white (88.5%), black (90.9%), and Hispanic (92.5%) recipients, primary cadaveric actuarial graft survival was reduced in black patients after two years. A major correction may have been the exclusion of noncompliant patients from a reanalysis of data, yielding five-year graft survival that increased from 64.6% to 66% for white patients and from 49.5% to 63% for black patients.

It has become increasingly apparent that economics and compliance may contribute to graft loss in poor (black and Hispanic) inner city kidney transplant recipients. With equivalent patient selection, equal survival for black and Hispanic kidney graft recipients is noted in some studies. For example, in a large inner city kidney trans-

plant program, Sumrani et al²⁵ reported that one-year actual graft survival was identical (70%) in whites, blacks, and Hispanics. It was reasoned that the more careful selection of recipients would negate the black-white difference in patient and graft survival after kidney transplantation. A similar outcome in blacks and whites was observed when immunosuppression was switched from azathioprine to cyclosporine. In this perspective, Dawidson et al²⁶ reviewed the outcome of 343 adult cadaver renal transplants performed from 1/1/82 through 10/01/88 in Houston, and found that three months post-transplant, blacks had inferior patient (89%) and graft (54%) survival compared to whites (97% and 71%, respectively) using azathioprine, but that both races had identical one-year patient (92%) and graft (76%) survival with cyclosporine. There are no data from which to compare differences related to race in matched groups of uremic diabetic recipients of renal transplants.

CONCLUSIONS

Inner city blacks and Hispanics receive initial renal consultation relatively late in the course of kidney disease, including diabetic nephropathy. The incidence and prevalence of diabetes mellitus and the microvascular complication of diabetic nephropathy varies by race: Blacks have

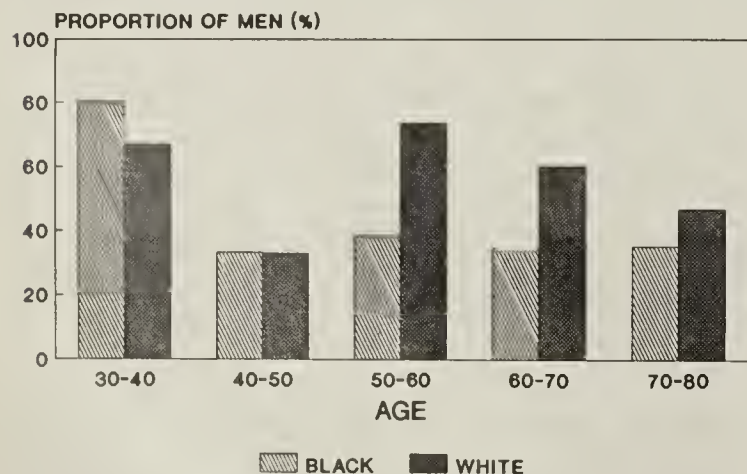


FIGURE 3. Gender of diabetic patients undergoing maintenance hemodialysis at 13 dialysis facilities in Brooklyn in 1986 (N = 197). Note that the majority of black patients are women, while the majority of white patients are men (data courtesy of Lowder et al²¹).

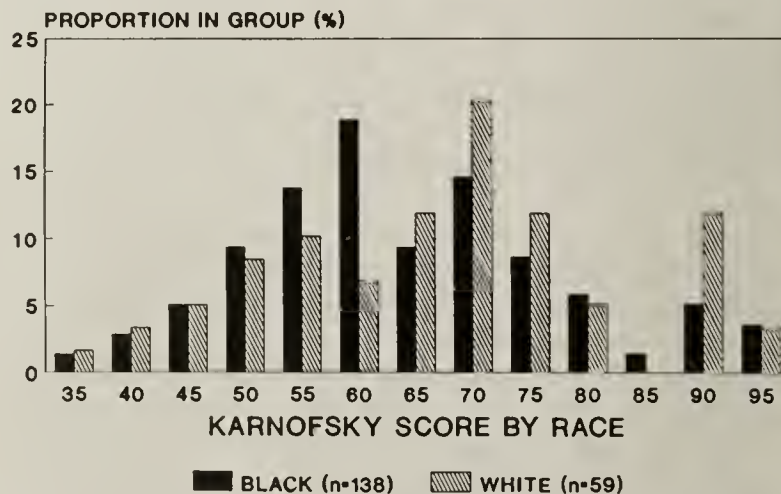


FIGURE 4. Karnofsky score of diabetic patients undergoing maintenance hemodialysis in Brooklyn according to race. Both blacks and whites have poor rehabilitation (good rehabilitation is indicated by a minimal score of 75) (data courtesy of Lowder et al²¹).

a distinctly higher rate than whites; Asians have a lower rate than whites. Evidence suggests that genetic factors strongly influence individual susceptibility to NIDDM within a race. Diabetes is 50 times more prevalent in adult Pima Indians in Arizona, for example, than in Mandan Indians in North Dakota. There are virtually no prospective data detailing the course of diabetic nephropathy in comparative subsets of populations or individuals grouped by race.

Inner city blacks and Hispanics manifesting ESRD due to diabetes have been treated by peritoneal dialysis, hemodialysis, and renal transplantation. In one large survey in Brooklyn, rehabilitation of blacks with ESRD due to diabetic nephropathy has been dismal. Survival of blacks undergoing maintenance hemodialysis is superior to that of whites for reasons that are undetermined. Previous reports that renal transplantation is less likely to be successful in blacks than in whites are now yielding to studies that suggest that when equivalent recipients are chosen, and cyclosporine is the main immunosuppressive drug, black and white recipients have the same patient and allograft survival for at least five years.

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Human immunodeficiency virus/acquired immunodeficiency syndrome nephropathy in the inner city

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Since the outbreak of the acquired immunodeficiency syndrome (AIDS) epidemic in 1981, there have been more than 150,000 reported cases in the United States.¹⁻³ Many of these cases have been in patients from inner city populations. In large cities such as New York, there have been more than 10,000 cases of AIDS; up to 500,000 persons in the New York metropolitan area have been report-

ed to be infected with the human immunodeficiency virus (HIV).¹⁻³

Many studies have found that populations of intravenous drug abusers have a 60-85% carriage rate for HIV.¹⁻³ Infection with this virus has been associated with a number of patterns of renal disease including acute renal failure and a unique form of glomerulopathy now called HIV nephropathy. The relationship of this glomerulopathy to the older entity of heroin nephropathy has been debated.¹⁻³

SPECTRUM OF HIV ASSOCIATED RENAL DISEASE

Early studies of patients with AIDS who had clinically

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apparent renal disease clearly showed a spectrum of renal lesions present in this population. The data from the 1984 study of Gardenswartz et al,⁴ which are typical of other studies, reported the following findings in 13 patients with proteinuria or renal insufficiency: acute tubular necrosis (ATN), in 3 patients; focal interstitial nephritis, 3; nephrocalcinosis, 3; renal cell carcinoma, 1; cryptococcal abscess, 1; glomerular lesions, 5.

A better overview of the problem can be gleaned from a recent autopsy review of 30 consecutive AIDS patients.⁵ This population of 26 males and four females, with a mixed racial background and a mean age of 39 years, included patients with a number of risk factors for AIDS (homosexuality, 19; intravenous drug abuse, 5; blood transfusion, 1; child of drug abuser, 1; unknown, 4). These patients had multiple opportunistic infections and neoplasms, as might be expected for a group with AIDS.

The clinical renal findings in these 30 patients included ATN in 16 patients, no renal diagnosis in 13 patients, and AIDS nephropathy in only one patient. Moreover, the histopathologic findings at autopsy included nine patients with ATN, eight with pathogens in the kidney, four with chronic tubulointerstitial nephritis (TIN), 13 with nephrocalcinosis, and one with AIDS nephropathy (Table I).

Clearly, a spectrum of renal findings is evident, and ATN, chronic TIN, and nephrocalcinosis are common findings. AIDS or HIV nephropathy has been found in 3% to 7% of unselected autopsy series.

ACUTE RENAL FAILURE

The course of patients with acute renal failure and AIDS has been described by a number of investigators.⁶⁻⁸ Rao et al⁷ have described the course of 23 patients. The most common precipitating factors for acute renal failure included medications (pentamidine, aminoglycosides, trimethoprim-sulfamethoxazole, and non-steroidal anti-inflammatory drugs), and pyrexia and dehydration superimposed on sepsis-hypotension-respiratory failure. All six patients with mild renal failure regained renal function. Of those 17 with severe renal failure (serum creatinine > 6 mg/dL), eight of the eleven who did not undergo dialysis died of renal failure, while five of the remaining six who did undergo dialysis regained renal function. Thus, dialysis support is indicated for the AIDS patient with acute renal failure.

HIV NEPHROPATHY

Several histologic patterns of glomerulopathy have been seen in patients with AIDS or HIV infection.^{1-3,7-10} These include minimal change pattern, glomerular mesangial hyperplasia, glomerulopathies associated with immune complex deposition presumed secondary to infec-

TABLE II. Clinical Features of HIV Nephropathy

Blacks
Often intravenous drug abusers
Substantial proteinuria, nephrotic syndrome
Renal insufficiency, rapid progression to end stage renal disease
Large kidney size

tion, and, most importantly, AIDS or HIV nephropathy. HIV nephropathy is a unique pattern of glomerulopathy in HIV infected patients characterized by substantial proteinuria and rapid progression to renal failure, and with characteristic ultrasonographic and renal biopsy findings. HIV nephropathy is a better term than AIDS nephropathy since this glomerulopathy may occur in patients with AIDS or AIDS-related complex (ARC), as well as in asymptomatic HIV carriers.¹¹

While HIV nephropathy has a prevalence of only 3% to 7% of unselected autopsy series, it is by far the most common lesion found in HIV infected patients undergoing renal biopsy. Most of the descriptions of HIV nephropathy have come from the study of inner city populations in New York, Miami, and Los Angeles. The classic clinical features of this entity have been described (Table II). The disease occurs predominantly in blacks and more often in intravenous drug abusers than in other HIV infected populations. It is associated with large amounts of proteinuria and the nephrotic syndrome. Patients often present with renal insufficiency or renal failure, and the progression to end stage renal disease is rapid. On ultrasonography the kidneys are found to be large and echogenic.

In a recent clinical study, our physician group looked at the epidemiologic characteristics of patients with HIV nephropathy versus an autopsy group with AIDS and with histologic proof of the absence of glomerular lesions.¹¹ The autopsy group was epidemiologically similar to the total population with AIDS seen at Columbia Presbyterian Medical Center over the time period of the study. The results shown in Table III clearly demonstrate the predilection of HIV nephropathy for blacks and intravenous drug abusers. Of interest is the significant percentage of Haitian non-drug abusers with HIV nephropathy in the University of Miami series. Moreover, HIV nephropathy has been extremely uncommon in San Francisco where most AIDS patients are white and homosexual.

Our recent series documents the high incidence of renal

TABLE III. Characteristics of Patients with HIV Nephropathy at Columbia Presbyterian Medical Center, 1986-1988¹¹

	HIV Nephropathy (N = 26)	Autopsy (N = 24)
Age (yr)	38	41
Sex (% male)	69	92
Race		
% Black	96	46
% Hispanic	4	33
% White	0	20
Risk factors		
% Intravenous drug abusers	42	17
% Homosexual	31	67
% Other	27	17

TABLE I. Pathologic Renal Diagnosis in 30 AIDS Cases at Autopsy

No pathology diagnosed	11
Acute tubular necrosis	9
Pathogens in kidney	8
Chronic tubulo-interstitial nephritis	4
Kaposi's sarcoma	1
Nephrocalcinosis	13
AIDS nephropathy	1

insufficiency, hypoalbuminemia, edema, and hypertension in the population with HIV nephropathy when compared to other AIDS groups (Table IV).¹¹

The kidneys of patients with HIV nephropathy, when viewed by ultrasonography, were large for the degree of renal failure (mean size 12.3 cm) and echogenic.

The course of HIV nephropathy usually includes rapid progression to renal failure. In an early study, Rao et al⁶ found the mean time from diagnosis to uremia was three to four months for patients with AIDS nephropathy with a creatinine clearance rate greater than 60 cc/min.⁶ It was 43.7 months for patients with heroin nephropathy with a similar clearance. In a more recent study, Rao⁷ followed 55 AIDS patients with HIV nephropathy. Of the 43 patients whose conditions progressed to end stage renal disease, 12 did not undergo dialysis and all died; of the 31 who did have dialysis, 26 died within three months of initiating dialysis. Thus, the benefits of providing dialysis support to the population with AIDS and HIV nephropathy are less than clear.

In our study of 26 patients with HIV nephropathy, the stage of involvement with the HIV infection proved to be the most important prognostic feature for survival (Table V).¹¹ Patients with AIDS and end stage renal disease have a very short survival. Patients with asymptomatic HIV infection can survive many years on dialysis. In our experience, all patients with true HIV nephropathy (the classic biopsy pattern) have gone on to develop AIDS eventually.

Whether this entity of HIV nephropathy is truly different from heroin nephropathy has been debated. Clinical and histologic data would suggest that they are distinct entities. Heroin nephropathy occurs exclusively in addicts, while only 33% to 50% of patients with HIV nephropathy are intravenous drug abusers. The pathology of heroin nephropathy is one of classic focal segmental sclerosis, as opposed to the collapsing glomerulopathy of HIV nephropathy. The progress to end stage renal failure is much more rapid in HIV nephropathy than in heroin nephropathy.

PATHOLOGY OF HIV NEPHROPATHY

The pathology of HIV nephropathy shows several features distinct from classic focal segmental glomerulosclerosis or heroin nephropathy.^{2,5} On light microscopy, diffuse global glomerular sclerosis and collapse is common, with striking visceral epithelial cell hypertrophy and large cytoplasmic vacuoles and resorption droplets. There are also severe tubulointerstitial changes with interstitial inflammation, edema, microcystic dilation of tubules, and severe tubular degenerative changes. On electron microscopy, tubulo-reticular inclusions are much more prevalent in the glomerular endothelium. While these may only be a marker for the presence of a severe viral infection, their

TABLE IV. Clinical Features of HIV Nephropathy (N = 26) vs AIDS Autopsy Group (N = 30)¹¹

	HIV Nephropathy	Autopsy Group
Serum creatinine (mg/dL)	5.4	1.0
Serum albumin (g/dL)	2.2	2.9
Edema (%)	62.0	8.0
Hypertension (%)	39.0	4.0

TABLE V. HIV Nephropathy at Columbla Presbyterian Medical Center—Stage of HIV Disease and Outcome¹¹

Stage/Outcome	N
At presentation of renal disease	
No symptoms	12
Early HIV infection	8
AIDS	6
At end of study	
Died	15
Alive with early HIV infection	7
Alive without symptoms	4
Dialysis status at end of study	
Required dialysis	19
Alive without dialysis	4
Died with end stage renal disease prior to dialysis	3

presence in a patient with classic light microscopic changes of HIV nephropathy makes the diagnosis quite certain.

PATHOGENESIS AND TREATMENT

The pathogenesis of HIV nephropathy is unknown.^{1-3,11} Speculation must take into account certain features: the epidemiologic data showing that the disease is more common in blacks and intravenous drug abusers; the unusual histologic features of collapsing focal glomerular sclerosis and the interstitial changes; and the fact that it can occur in patients who have no infections or other manifestations of HIV infection at the time of their glomerulopathy. Theories on the pathogenesis of HIV nephropathy include acute renal hemodynamic alterations, toxicity to the visceral epithelial cells, and possibly toxicity to the tubules themselves.^{1-3,11} HIV core protein (p-24) and proviral DNA have been localized to the tubular cells and visceral epithelial cells, but their role in the pathogenesis of HIV nephropathy is unclear.¹²

The treatment of this disease also remains enigmatic. So far, there is no conclusive evidence that treatment with zidovudine (AZT) or other agents will delay the appearance of AIDS in the asymptomatic population with HIV nephropathy. Dialysis and support seem appropriate for patients with HIV nephropathy without the full-blown AIDS syndrome. Once AIDS has developed, whether dialysis support will prolong useful life is a matter open to debate.^{7,11}

DIALYSIS AND TRANSPLANTATION

Recently, there has been great concern about the risk of HIV infection in dialysis populations and the potential spread of HIV to staff and hospital workers.¹⁻³ Inner city populations are clearly at higher risk of having AIDS, ARC, and asymptomatic HIV infection. To date, however, even in these populations there has been no evidence for spread of HIV between dialysis patients or between patients and staff.^{2,3} Transplant patients may theoretically be at risk of developing HIV infection from blood transfusions or the allograft itself, or they may be asymptomatic carriers of the virus at the time of transplantation. Blood products, donor organs, and recipients are now all screened for HIV infection. Nevertheless, HIV infection has been reported in transplant patients receiving kidney, liver, bone marrow, and heart transplants.¹³ The types of

opportunistic infection, their time course after transplantation, and the patients' immunologic responses to them should rapidly alert the clinician to cases of post-transplant HIV infection.¹³

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Poverty, ethnicity, and dialysis services in Israel

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Many countries face the problem of providing dialysis for the poor, which is not a concern in the case of the affluent. In the United States, the principal lack of adequate dialysis appears to be among the urban black population. The evidence is somewhat indirect, but there is a shortfall in the numbers of blacks on dialysis in the large northern cities of the United States when compared with estimates of the incidence of end stage renal failure in blacks in the southern states. In the United Kingdom, there has also been a serious lack of dialysis facilities for years, although the advent of continuous ambulatory peritoneal dialysis (CAPD) has provided a bureaucratically convenient solution to the shortage of hemodialysis sites. Still there seems to be a shortfall of diabetics, possibly related to physicians' attitudes. In Israel, a small country, isolated in a sea of implacable enmity of the surrounding Arab states, with the qualified exception of Egypt, there are similar problems—lack of funds and urban and rural poor and minorities. In this paper, we look at the way these problems have been solved and are being solved in Israel as compared to other countries.

SOCIAL AND POLITICAL BACKGROUND

This paper deals with Israel proper and not with Judea, Samaria (the West Bank), and the Gaza Strip. For the purposes of this work, Jerusalem is West Jerusalem, although a portion of the dialysis population comes from predominantly Arab East Jerusalem.

Israel is a small country—at its narrowest it is eight

miles wide and 300 miles long. Even with Judea and Samaria included, it is only 37 miles wide between the river Jordan and the Mediterranean Sea. The number of inhabitants in April 1990 was 4.6 million, 81.5% being Jewish and 18.5% minorities (Moslems, Christians, Druze, and other sects) (personal communication, Israel Consulate, New York, September 1990).

The major conurbation is an area from about 20 miles north of Tel Aviv to 20 miles south of Tel Aviv containing 1.5 million inhabitants. The city of Tel Aviv itself suffers from central urban decay with an increasing percentage of elderly, the younger inhabitants having migrated to the suburbs. There are many pockets of poverty in the southern suburbs, particularly Hatikvah, where the population is predominantly of Oriental Jewish origin and where there is a higher crime rate. In Jaffa there is poverty among both Arabs and Jews, together with revitalization with avant-garde tourist galleries. West Jerusalem also has suburbs of poverty neighboring affluent suburbs: the Musrarah quarter abutting "no-mans land" in the pre-1967 era is an example of poverty and substandard housing now being replaced. Katamon is one of several south Jerusalem slums that have poverty, crime, and a lack of adequate education as common features.¹ Haifa has several slum areas, mainly Arab, but also with a mixture of Jewish inhabitants. Some have been evacuated as part of urban renewal programs, and others have been cosmetically upgraded in part.² In Beersheva, the southernmost large city, there were at least four quarters that were slums with serious communal problems. At least one of them has been upgraded into a desirable urban area.

There is also much rural poverty. Many of the interdependent village (Moshav) farmers are in dire financial straits, with huge burdens of debt and despair. The Arab villages in the little triangle opposite to Hadera and Na-

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tanya as well as those in lower and upper Galilee have poverty, unemployment, and lack of basic facilities such as sewers, and, consequently, the inhabitants seethe with nationalist sentiment. In the Negev, the Bedouin have largely been rehoused in towns which they run themselves. They are not poverty stricken and there are no slums, quite the contrary, in these new towns.

HEALTH SERVICES IN ISRAEL

Health services function as a two-tier health system: a major public service open to all through either the Ministry of Health or the various health funds, and a private service with several private hospitals such as Hadassah in Jerusalem, Assuta in Tel Aviv, and Elisha in Haifa. Unfortunately, there is a hybrid tier, whereby someone with money can see a physician from a public hospital in his private office and then be "facilitated" in getting preferential treatment without waiting. This is referred to as "black medicine" in contrast to "community medicine," which is the regularly available service. Many of the large independent hospitals such as Hadassah and Shaarei Zedek in Jerusalem receive government or Workers Sick Fund subsidies, and are really independent in some areas only.

DIALYSIS IN ISRAEL

All major hospitals have regular dialysis facilities, and there are also a few private clinics for foreign tourists. Dialysis for citizens of Israel, Jewish or minority, is provided essentially free of charge and without limit, even to those without insurance. Patients may be offered hemodialysis in a unit or at home, or chronic ambulatory peritoneal dialysis (CAPD), depending on facilities.

Patients are placed on dialysis at the hospital to which they will be admitted for medical treatment. There they undergo a shunt operation. A "private" paying patient may gain access to dialysis somewhat more quickly than a poor patient, but this is rarely of any consequence as most of the dialysis units are in-hospital units, and the difference between private and public patients may be a wait of a month or two at most. The type of dialysis—hemodialysis or CAPD—will depend on the doctor/patient joint decision, and as far as can be ascertained is not influenced by financial considerations.

The poor are not discriminated against. Any Israeli entering end stage renal disease can receive one or another form of dialysis or be offered transplantation; the vast majority of patients are poor. Because the poor areas are equipped with government and Sick Fund clinics, the poorer patients essentially experience the same types of delays in diagnosis and treatment as the wealthier patients. There may be differences in educational background, so that the better educated and often wealthier patients may go to see a doctor sooner than those less educated.

The total number of patients on dialysis in Israel in April 1990 was 1,457 out of a total population of 4.6 million, ie, 316.7 per million (Tables I, II). For a population the size of the United States, this would give 77,707 patients—slightly less than are actually receiving regular dialysis in the United States and more than in the United Kingdom.

TABLE I. Age Distribution of the Israeli Population Divided Into Jews and Minorities*

	Jews	Minorities
Total	3,494,000 (100%)	568,700 (100%)
Under 20 yr	1,336,000 (40.1%)	333,000 (58.6%)
Over 55 yr	682,300 (19.5%)	31,300 (5.5%)

* Source: Israel Government Year Book for 1985. Jerusalem, Central Statistics Bureau, 1986.

There is no evidence that the poor are deprived of dialysis. It is possible that the remnants of the Bedouin who are still nomadic get suboptimal care, but the vast majority receive regular clinic care and can undergo dialysis without any problems. No Israeli Moslem, Christian, or Druze Arab is denied dialysis or other therapy because he is an Arab.

On the other hand, 18.5% of the population are minorities (mainly Arabs), but of those on dialysis only 12.6% are minorities. Is this difference true evidence of some discrimination? The answer appears to be equivocal. The major age groups requiring dialysis for end stage renal disease are those 55 years and over. In the Jewish population there are proportionately three times as many people over the age of 55 as among minorities (Table II). Thus it would appear that, if anything, the Jewish population is not over-represented in the dialysis population. On the other hand, in the Jewish population there is a moderate incidence of familial Mediterranean fever (FMF) affecting younger and middle aged adults, giving rise to end stage renal disease (ESRD), and this tips the balance back. There are some one and a half times more minorities under the age of 20 than there are Jews (Tables I, II). Aside from FMF, ESRD is relatively less common in the under 20 years' age group. Even so, in the only childrens' hospital dialysis unit in West (Jewish) Jerusalem, there is a preponderance of Arab children on dialysis. In Beer-sheva and in Galilee, where there are large Arab populations, there are proportionately more Arabs on dialysis (Tables III, IV).

It thus seems that not only do the poor not suffer whether they are urban or rural, but also that the minorities probably do not suffer. Indeed, there are 282 Arabs per million Arab population on dialysis. No Arab country even comes near this figure.

Transplants of all types—kidney, heart, liver, and pancreas—are carried out in major hospital centers in Jerusalem, Tel Aviv, and Haifa. The donors are invariably Jew-

TABLE II. Live Births per Thousand Population in Israel, and Ethnicity, 1985*

Live Births per Thousand Population	
Jews	21.6
Urban	21.3
Rural	23.7
Arabs	32.3
Urban	30.9
Rural	40.7

* Source: Israel Government Year Book for 1985. Jerusalem, Central Statistics Bureau, 1986.

TABLE III. Details of Patients on Dialysis in Various Dialysis Units in Israel in April 1990*

Hospital	Total	Jews	Minorities	%
Beilinson	65	65	0	0
Hadassah T. A.	84	80	4	4.7
Reines T. A.	25	25	0	0
Tel-Hashomer	103	102	1	0.97
Hasharon	123	116	7	5.7
Sinai Hotel	13	12	1	7.69
Wolfson T. A.	106	105	1	0.94
Laniado	18	16	2	11.11
Meir	100	90	10	10
Hilel-Yaffe	34	25	9	26.47
Kaplan	70	70	0	0
Assaf Harofe	76	75	1	1.36
Ashkelon	54	54	0	0
Sorokka	105	82	23	21.9
Hadassa Jer.	64	43	21	32.8
Sha'arei Tzedek				
adults	33	28	5	15.16
children	28	10	18	64.2
Rambam Haifa	89	73	16	17.98
Carmel	88	81	7	7.9
Rothchild	43	34	9	20.9
Elisha	5	5	0	0
Nahariya	48	32	16	41.6
Nazaret	13	0	13	100
Affula	34	22	12	35.2
Tiberias	18	15	3	16
Zaffed	18	13	5	27
Total	1,457	1,273	184	12.6

* Source: Israel Dialysis Registry (personal communication to Prof J. Ben-Ari, April 1989).

TABLE IV. Patients on Dialysis by Region and Ethnicity in Israel, April 1990*

Area	Total	Jews	Arabs	Arabs as % of Total
Tel Aviv area	506	492	14	2.8
Israel coast and triangle	152	131	21	13.8
Med coast south	200	199	1	0.5
Beersheva	105	82	23	21.9
Jerusalem				
adult	97	71	26	26.8
children	28	10	18	64.2
Haifa	225	193	32	14.2
Galilee	131	82	49	37.4
Total	1,457	1,273	184	12.6

* Based on data from Table III.

ish and not Moslem, in view of the religious prohibitions in Islam of removing body parts post mortem. The recipients are chosen according to tissue typing, irrespective of race, religion, and ethnic group. This has given rise to bizarre situations in the current Arab revolt or *intifada*, in which West Bank Arabs have received transplanted organs from the victims of Arab terror.

In conclusion, it appears that neither race, nor religion, nor wealth influences the opportunity for patients with end stage renal disease to get dialysis in Israel. Israel has the highest number of Arabs (expressed per million) on dialysis in the world.

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Pulmonary-renal syndrome

Its clinicopathologic approach in 1991

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While studying the histopathology of the lungs of victims of the 1919 influenza pandemic, Dr Ernest W. Goodpasture¹ came across a 19-year-old patient who had had hemoptysis, azotemia, and proteinuria associated with intra-alveolar bleeding and inflammatory glomerular changes. This association of lung hemorrhage and renal failure, now known as "pulmonary renal syndrome (PRS)," remained ignored until it was rediscovered by Stanton and Tange² in 1959. Believing that the patients they described had the same disease process as that reported by Goodpasture, Stanton and Tange coined the eponym "Goodpasture's syndrome," and this subsequently gained universal

acceptance.

However, Goodpasture's syndrome is but one of many entities mediated by immune, infectious, and toxic-chemical phenomena that can produce PRS.²⁻⁸ Independent of cause(s) and mechanism(s), PRS constitutes a serious and potentially lethal medical emergency which may rapidly and irreversibly lead to ventilatory and renal failure without early and aggressive intervention.²⁻⁸ The term PRS is currently used synonymously for acute glomerulonephritis and pulmonary hemorrhage, idiopathic Goodpasture's syndrome, immune alveolar hemorrhage, and diffuse pulmonary hemorrhage syndrome.²⁻⁸ The numerous immune and non-immune mediated conditions that can lead to PRS are summarized in Table I. Undoubtedly, the three major entities of this list are Goodpasture's syndrome, Wegener's granulomatosis, and idiopathic, rapidly pro-

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TABLE I. Most Frequent Entities Producing Pulmonary Renal Syndromes

Antibasement membrane antibody (ABMA) diseases
Goodpasture's syndrome
Idiopathic rapidly progressive glomerulonephritis (IRPGN)
Immune complex (IC) diseases
Specific vasculitis (systemic lupus erythematosus, Henoch-Schönlein purpura, subacute bacterial endocarditis)
Berger's disease
Cryoglobulinemia
Idiopathic rapidly progressive glomerulonephritis
Antineutrophil circulating antibody (ANCA) diseases
Wegener's granulomatosis
Polyarteritis nodosa
Idiopathic rapidly progressive glomerulonephritis
Presumed to be immune mediated*
Idiopathic rapidly progressive glomerulonephritis
Sarcoidosis
Sarcoid-like granulomatosis
D-penicillamine
Trimellitic anhydride
Non-immune mediated
infections (<i>Legionella pneumonia</i>)

* In these entities, ABMA, IC, ANCA, antinuclear antibody (ANA), and anti-double-stranded DNA tests are negative; the third and fourth complement components (C3 and C4) and total complement (CH50) are normal.

gressive glomerulonephritis (IRPGN).

Pulmonary renal syndrome is rather uncommon, with 40% to 60% of cases occurring in patients with a vasculitic background.⁵⁻⁶ Additionally, 15% to 30% of patients have idiopathic, rapidly progressive glomerulonephritis, in which glomerular lesions compatible with, and extrarenal manifestations of, vasculitis may eventually develop.^{4,9} Thus, in 50% to 80% of cases, PRS is dominated by some form of vasculitis. Twenty percent to 40% of PRS is due to what in general terms is known as antiglomerular basement membrane antibody (AGBM) disease, which encompasses Goodpasture's syndrome and IRPGN.^{5,6,10-13} Other authors¹²⁻¹⁴ have estimated that PRS constitutes either 5% percent of all cases of glomerulonephritis (GN) or 23% of crescentic GN; another 26% of crescentic nephritis cases involve IRPGN without systemic vasculitis. The other 51% of cases were associated with systemic vasculitis, of which only 55% were confirmed by tissue diagnosis. In a more recent study, 72% of crescentic GN cases were associated with vasculitis in which Goodpasture's and Wegener's syndrome are included.⁹

Hundreds of cases of Goodpasture's syndrome and of Wegener's granulomatosis have been reported since they were first described.⁷⁻¹⁷ A discussion of the epidemiology and clinical characteristics of these conditions is beyond the scope of this review and has been published elsewhere.⁷⁻²³ Here, only the pathogenetic, diagnostic, and therapeutic aspects of PRS are covered. Comments on this vast and complex subject are directed here primarily to general practitioners and internists, and other physicians caring for critically ill patients.

PATHOGENESIS

Although the etiology of most PRS remains unclear, the knowledge of its pathogenesis has advanced considerably.²⁴⁻³¹ While experimental models of glomerulonephri-

tis induced by immunization with foreign renal antigen(s) have been in existence since the 1930s (Masugi nephritis),¹⁵⁻¹⁶ autoantibody mediation of rapidly progressive glomerulonephritis (RPGN) (ie, Goodpasture's syndrome) constitutes a recent observation.^{15,25-28,31-34} These studies demonstrated antibasement membrane autoantibody targeted to collagen IV protomer, the building block moiety of the glomerular capillary basement membrane. The antibody specifically binds the non-collagen 1 domain of the alpha-3 chain.^{33,34} Because of collagen's tridimensional and helical configuration, Goodpasture's autoantigen is seemingly sequestered within collagen IV components.^{33,34} It is hypothesized that infections, toxic agents (eg, cigarette smoking, hydrocarbon inhalation), and genetic factors may help uncover the antigen which, when recognized and processed by immunocompetent cells, promotes synthesis of autoantibody and autoimmune inflammatory pulmonary-renal disease.^{33,34}

Similarly, foreign and cryptic endogenous antigens may trigger systemic and/or in situ formation of immune complexes, producing multisystemic disease, particularly of kidneys and lungs. Thus, PRS is also mediated by formation-deposition of immune complexes (IC) within these organs and tissues.^{33,37-54} In addition, autoantibodies that react with autoantigens contained in the cytoplasm of normal polymorphonuclear and mononuclear leukocytes, the so-called "anti-neutrophil cytoplasmic antibodies," or ANCA, develop in some forms of PRS.^{33,37-54} These autoantibodies are specific markers of, and effectors involved in, the pathogenesis of Wegener's granulomatosis (WG) and, to a lesser extent, of polyarteritis nodosa (PAN), and of some forms of idiopathic, rapidly progressive glomerulonephritis (Table I).^{33,40-44,46,52,54} Thus, leukocytes possess the so-called Wegener's antigen⁴³ which, in a manner akin to that postulated for antibasement membrane antibody disease, requires immunologic recognition to induce autoimmune disease. Highly sensitive assays, described later, detect serum ABMA and ANCA by their reaction with antigens contained in capillary basement membranes and leukocytes of patients and normal controls.^{40,42,46,49,50}

Moreover, Lockwood and associates⁴¹⁻⁴³ demonstrated in vitro the existence of Wegener's antigen in the renal glomerulus. The presence of the antigen in endothelium and epithelium (but not in mesangium) strongly supports the direct effect of ANCA on these cells—the precise sites where crescentic and necrotizing glomerulonephritis characteristic of PRS develops. Thus, as described below, the appropriate diagnosis, prognosis, and therapy of PRS depends heavily on the early tissue and serologic evaluation of the patient. Kidney and lung biopsy samples studied by immunohistopathology and electron microscopy can discriminate among the several causes of PRS by correlating the histologic findings with the type and distribution of immune deposits. In addition, the ultrastructural pathology and localization of specific antibody and of immune aggregates can be sharply defined.

Most examples of PRs (Table I) share similar glomerular abnormalities by light microscopy, from focal segmental to diffuse extra-capillary proliferative lesions, with some form of necrotizing and/or crescentic, rapidly progressive glomerulonephritis being the most common,

albeit nonspecific, histopathologic denominator.^{7,10,11,13,27,29,33,55} Immunofluorescence microscopy of kidneys, lungs, and polymorphonuclear neutrophil cells, on the other hand, separates three immunopathologic patterns seen in PRS.

First, smooth linear deposits along the basement membrane of the glomerular capillary wall of Bowman's capsule, tubules, and alveolar capillaries may be present. Goodpasture's syndrome, the prototypical ABMA disease, shows these findings.^{27,28,34,56} The diffuse spatial distribution of Goodpasture's antigen and the proximity among antigenic sites may produce the continuous (or interrupted) bright ribbon-like deposits with fluorescein-labelled antibody.

Second, a nodular or granular immunofluorescent appearance of antigen-antibody complex disease is seen in IC-mediated PRS.^{30,31,35,36,55} In ABMA- or IC-mediated processes, IgG, serum complement components, fibrin-fibrinogen related antigens, platelet antigens, nucleoproteins, fibronectin, and other proteins, appear in the glomerular deposits.^{30,31,35,36,56} In ABMA and IC diseases antibody can be eluted.^{28,31} In an occasional case of IC disease, antigen is retrieved from kidney and plasma (ie, nucleoproteins in systemic lupus erythematosus), or IC can be detected in the circulation.^{31,35,36} In ABMA disease, antigen is consistently isolated from the collagenase-solubilized fraction of the glomerular basement membrane.^{33,34} In addition, the serum of a patient with Goodpasture's syndrome contains autoantibody to basement membrane (of lung and kidney), which can be quantitated.

Injection of ABMA into primates induces glomerulonephritis.⁵⁷ Contrary to the little clinical value of measuring circulating IC, detection of antiglomerular basement membrane antibody in serum is *sine qua non* to definitive diagnosis of classical Goodpasture's syndrome.^{31,32} Unfortunately, detection-quantitation of ABMA is not routinely performed in the clinical setting. Its prolonged turnaround time hinders its value as an early therapeutic indicator.³² A recently developed procedure allows specific and reproducible early diagnosis of ABMA disease, mainly Goodpasture's syndrome, in hours or minutes.⁵⁸

The third immunopathologic pattern observed in PRS mediated by ANCA displays microgranular cytoplasmic and perinuclear findings on indirect immunofluorescence of polymorphonuclear and mononuclear leukocytes.^{37,40,54} It remains unclear why autoantibodies to neutrophilic cytoplasmic antigens develop. Despite the fact that normal or pathologic destruction of white blood cells should provide readily available cell material, the resident cryptoautoantigens seemingly remain unrecognized by the immune system. Whether antigens do not reach immunocompetent cells, or subliminal physicochemical alterations occur that preclude recognition, remains unknown. Molecular changes, disruption of disposal mechanisms of cytoplasmic antigens, or combinations thereof, induced by foreign and/or endogenous stimuli may lead to autoimmunity. Occasionally, the presence of minor amounts of renal immune deposits and a positive IC assay in ANCA-mediated RPGN may represent the nonspecific trapping of immunoglobulins or IC-like circulating protein aggregates. Nevertheless, efforts at looking for renal

and lung fluorescence or circulating immune complexes in Wegener's granulomatosis have been inconclusive.^{40,42,48,49,51}

As suggested by findings in other diseases,^{33,55} activation of neutrophils occurs on contact with microorganisms or their products; actually, endogenous (integrins) and foreign toxic substances may uncover and/or externalize antigen(s) or cell surface receptors. The latter, on neutrophils and monocytes, as well as endothelium and epithelium of lung and kidney, become the target of autoantibodies. Thus, ANCA synthesized in Wegener's granulomatosis presumably bind to intracellular/surface protein antigens, forming true *in situ* IC readily detected by indirect immunofluorescence. This hypothesis presumes the formation of O₂ radicals catalyzed by the enzyme nicotinamide adenine dinucleotide phosphate hydrogenase (NADPH) as has been demonstrated in activated leukocytes. The resulting superoxide dismutates and generates hydrogen peroxide which, in myeloperoxidase-related catalysis, reacts with chloride to form hypochlorous acid, or hypochlorite. The latter product, released in leukocyte phagosomes as well as systemically, produces highly toxic chloramine. Concurrently, leukocyte's azurophil granule enzymes (particularly myeloperoxidase and serum proteinases such as elastase) are incorporated in vacuoles and released externally. This process occurs frequently *in vivo*, where swift proteinase-inhibitors (serpins) maintain proteinase activity under constant control. ANCA are specific for protein enzymes, primarily elastase, located in the granules. Binding of the antibody with the proteinase may impede the effect of the serpin, promoting persistent vessel and tissue damage in association with superoxide and chloramine formation (Figs 1, 2, 3).⁵⁸ Subsequently, the process may escalate because complement and other inflammatory mediators are recruited locally or systemically, with ensuing necrotizing and proliferative-crescentic glomerulonephritis.^{31,33,35,36}

While renal-pulmonary lesions in Wegener's granulomatosis and polyarteritis appear devoid of specific fluorescent characteristics, neutrophils light up brightly with antiserum to ANCA. ANCA lyse native neutrophils, as documented by the finding of Ig-coated intracytoplasmic organelles in Wegener's lesions.^{45,46,49,53,55} Additionally, the neutrophil count and turnover is significantly increased during the active phase of the disease.^{59,60}

Antigens involved in the determination of ANCA are

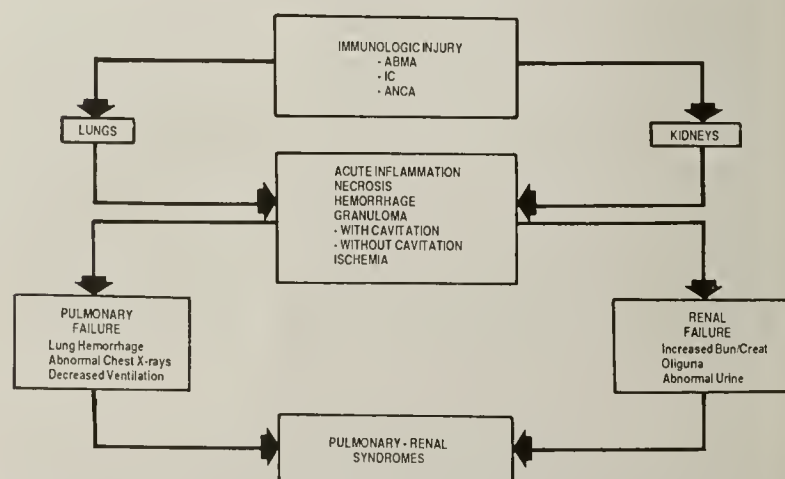


FIGURE 1. Summary of pathogenesis in pulmonary renal syndrome.

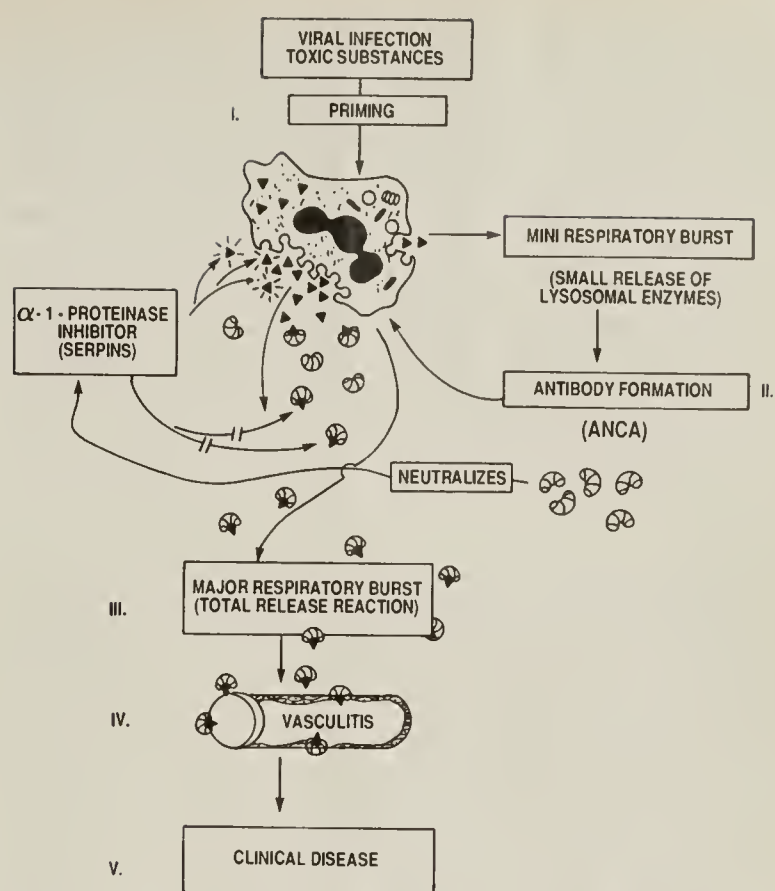
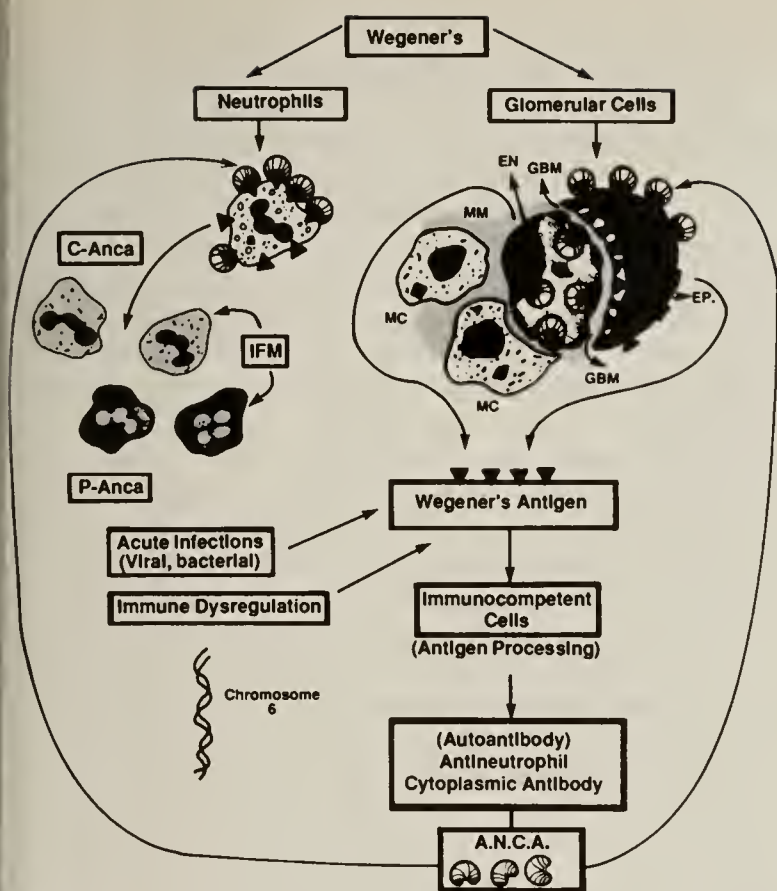


FIGURE 2. Pathogenesis of anti-neutrophil cytoplasmic antibody (ANCA)-mediated PRS. Left, It has been hypothesized that blood neutrophils and glomerular epithelial and endothelial cells possess the so-called Wegener's antigen. One possible role of ANCA may not only be to damage cells but to protect azurophil-granule content/elastases and myeloperoxidases from destruction by serum proteinase inhibitors (serpins), allowing the enzymes to maintain their tissue pro-inflammatory and destructive properties. Right, Leukocyte respiratory burst, autoantibody (ANCA) formation, and possible neutralization of serum protein inhibitor (serpin) by ANCA. Presumably, proteinase bound to ANCA remains pro-inflammatory and contributes to development of vasculitic lesions.

isolated from sonicated normal neutrophils suspended in acid buffer;^{42,61} the antigen-containing supernatant is used to coat microtiter plates, to which ¹²⁵I-goat antihuman IgG is added and the radioactivity quantitated in a gamma counter. The acid extract is also subjected to gel filtration and high performance liquid chromatography fractionation.⁴² Of the several subfractions obtained,

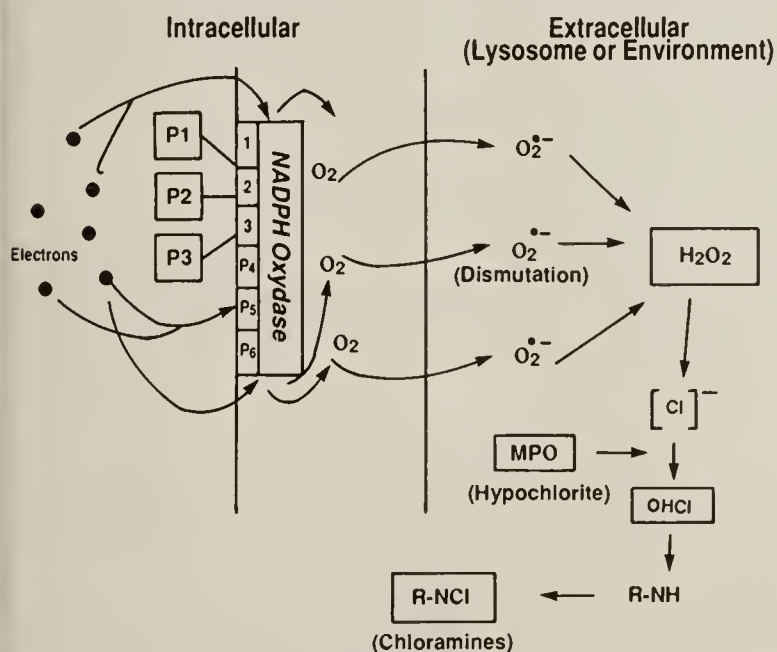


FIGURE 3. Pathogenesis of anti-neutrophil cytoplasmic antibody (ANCA)-mediated pulmonary renal syndrome. White blood cell respiratory burst.

those weighing 100, 6, and 2 kD have been studied. Sera from Wegener's patients bound to all three, whereas those from cases of microscopic polyarteritis nodosa reacted only with the heaviest (100 kD) peak. A monoclonal antibody raised against the 6 kD protein interacted with all three fractions. Recently, others have claimed that the specific Wegener's antigen is a 29-kD cytoplasmic protein fraction of neutrophils.^{44,62}

It stands to reason that detecting ANCA in certain patients with PRS has important diagnostic implications and will closely reflect disease activity. It is within this context that the clinical application of ANCA has become highly successful, allowing early diagnostic accuracy and rational therapy of Wegener's granulomatosis.^{33,43,52,53} This is reinforced by the fact that kidney and lung biopsy usually demonstrate vasculitis lesions compatible with but not specific for Wegener's granulomatosis.^{4,6,7,10,17,18,63,64}

DIAGNOSIS

The differential diagnosis of a patient with hemoptysis who is found to have renal failure may be difficult. Lung hemorrhage may or may not be associated with hemoptysis, and hemoptysis may develop during almost any lung disease, of which the non-immune mediated conditions are more frequent than the immune mediated processes and must be considered first. Occasionally, however, kidney failure, as defined by elevated serum creatinine, occurs in these cases and leads clinicians to entertain the diagnosis of PRS. Conversely, patients with preexisting

renal failure may develop hemoptysis due to lung infections or pulmonary edema. In such instances, the radiologic changes induced by aspirated blood may be indistinguishable from those resulting from alveolar filling secondary to pulmonary edema or to uremia itself. Although clinically similar, non-immune mediated conditions should be considered as a pulmonary-renal-like syndrome, since the therapeutic approach is substantially different from that of a true PRS. Renal failure associated with *Legionella* pneumonia or with any form of necrotizing pneumonitis exemplifies this situation (Table I). Perhaps subacute bacterial endocarditis should be considered in this category; however, the associated RPGN will respond to corticosteroids and appropriate antibiotic treatment.

One must always keep in mind that not all lung hemorrhages are due to immunologic phenomena, and that the association of alveolar bleeding with renal failure constitutes PRS until proven otherwise. The real challenge to the physician is to make diagnostic and therapeutic decisions in the midst of a rapidly deteriorating clinical situation. The patient with PRS characteristically has severe hypoxemia, alveolar hemorrhage, respiratory failure, and acute renal failure, and requires both dialysis and ventilatory support. In this setting of simultaneous diagnosis and treatment, the physician must carefully balance the benefits and risks of invasive but useful investigations, such as lung and renal biopsies, and potentially dangerous but life saving treatments, including intravenous corticosteroids and immunosuppressive agents.

Patients with PRS present with many nonspecific findings (Table II).^{3-8,17,18,63-65} These abnormalities may occur sequentially or concurrently and for extended periods, and may be the sole clinical manifestation of PRS. Lung involvement is accompanied by hemoptysis, anemia, and pulmonary infiltrates with rapidly progressive hypoxemia. Oliguria, nephritic urinary sediment (hematuria, proteinuria, red blood cell casts, leukocyturia), and increasing serum creatinine reflect the nephropathy. Hemoptysis, like hematuria, is quantitatively variable, non-specific, and therefore unreliable. Minor hemoptysis with massive and diffuse intra-alveolar hemorrhage that produces a purely alveolar or alveolar-interstitial radiograph-

ic pattern, frequently occurs. It is most important at this stage to determine whether the patient has true alveolar hemorrhage or another alveolar space filling process (eg, pulmonary edema, pneumonic infiltrates, pulmonary embolization), particularly in patients with unrecognized renal failure.^{3-8,21,63-65} The circumstances in which the hemoptysis and the radiographic changes have occurred must be evaluated in deciding if the roentgenographic abnormalities correspond to frank alveolar hemorrhage (see below). Lastly, general blood and microbiology laboratory tests (complete blood cell count and platelet counts, chemical profiles, creatinine levels, and electrolytes) and serologic studies must be routinely used.

The immediate diagnostic value of tests for antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid (A-dsDNA), serum complement (C3, C4, CH50), ANCA, and ABMA is low due to the time needed to obtain test results; however, it is important to always obtain these tests in the initial work-up of a PRS patient. Ideally, it is desirable to have such results early for timely therapeutic intervention, but in reality, aggressive therapy must sometimes be started before these results are reported, in order to attempt to arrest a rapidly progressive condition. Because lung hemorrhage, glomerulonephritis, and vasculitis frequently occur together, manifestations of both processes should be carefully scrutinized by clinical history, physical examination, laboratory studies, and histopathology. Once preliminary data have been obtained, the scenario with these seriously ill patients is usually one of multiple subspecialty consultation. A summary of the diagnostic work-up and therapy of PRS is presented in Figure 4.

Generally, the pulmonary condition is best evaluated and handled by determination of arterial blood gases and by assisted ventilation if warranted by clinical manifestations and low O₂ saturation rate. Sequential roentgeno-

TABLE II. Common Clinical and Laboratory Manifestations of Pulmonary Renal Syndromes

Malaise
Fever
Cough
Shortness of breath
Hemoptysis
Oliguria
Hematuria
Arterial hypertension
Rash
Arthralgia
Sinusitis
Lung infiltrates on chest films
Anemia
Increased erythrocyte sedimentation rate
Azotemia
Elevated serum creatinine level

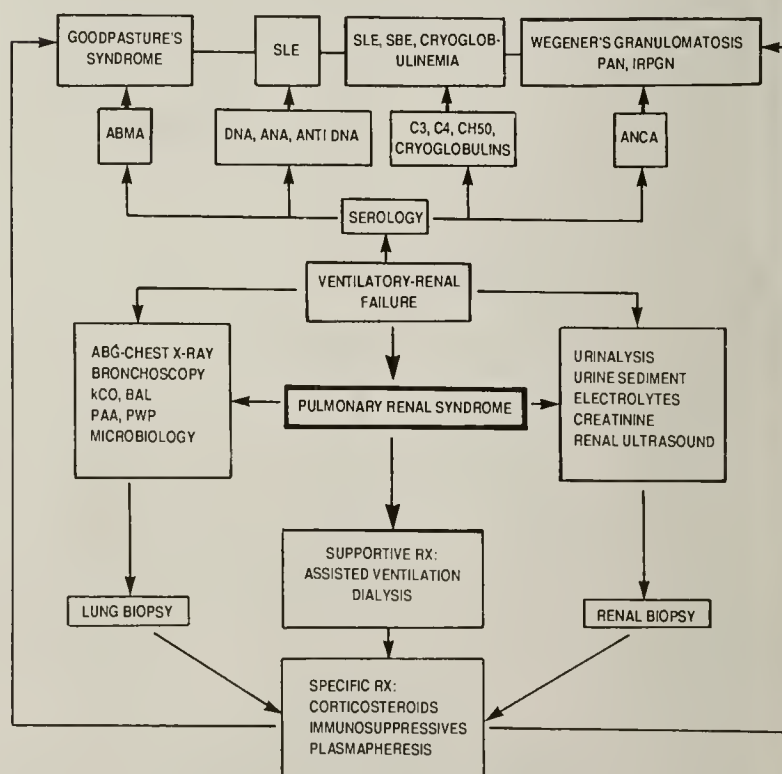


FIGURE 4. Summary of diagnostic workup and therapy of pulmonary renal syndrome.

grams with concurrent measurements of hemoglobin and hematocrit are helpful. Active lung bleeding with or without hemoptysis drops the hemoglobin concentration by 2 to 4 g/dL within 24 to 48 hours. Measurement of lung carbon monoxide uptake (kCO) should be considered. Increments of 30% or more over 48 hours, or a very high value in the absence of baseline information, is consistent with recent intra-alveolar hemorrhage. This test is based on the uptake of carbon monoxide by normal red blood cells within vessels and in the bronchoalveolar tree, where they may have extravasated.⁶⁵ Bronchoalveolar lavage, a procedure feasible in most individuals, may return bloody effluent which, by 48 hours, may contain large quantities of hemosiderin laden macrophages. The amount of intracellular pigment and the severity of the hemorrhage can be roughly correlated. Fluid can be stained and, together with blood, can be cultured to detect infection. Other useful diagnostic procedures include echocardiography, pulmonary wedge pressure measurements, coagulation studies, ventilation perfusion lung scan, pulmonary artery angiography, and computed tomography of the chest.⁶ Lastly, lung biopsy remains a controversial issue that will be discussed in more detail.

The diagnosis of renal involvement requires an accurate history and physical examination, as well as the general laboratory tests mentioned earlier. The urinalysis, and particularly the microscopic sediment examination, is crucial to determining the presence of inflammatory changes—ie, hematuria, red blood cell casts, nephritic-nephrotic range proteinuria (4+ or ≥ 3.5 g/24h), fatty casts, free fat globules, mulberry cells, and maltese crosses. Frequently, RPGN and vasculitis will show sediments that contain elements of nephritic, nephrotic, and chronic renal failure features, the so-called “telescoped sediment”; this is due to the relapsing nature of the lesion. The diagnosis of renal failure should be based on the elevation of serum creatinine levels rather than blood urea nitrogen, in addition to the serologic evaluation (Table III, Fig 4).

The rapidly progressive nature of the glomerulopathy usually requires an early kidney biopsy. Necrotizing crescentic glomerulonephritis with linear fluorescent deposits of IgG (or other immunoglobulin isotypes) along the cap-

illary walls makes the diagnoses of Goodpasture's syndrome and ABMA-mediated RPGN likely, whether or not confirmed by circulating ABMA. Tissue-fixed ABMA (host immunoglobulins, Ig) are easily detected by direct (fluorescein labelled anti-human antibody) or indirect immunofluorescence (using a “sandwich technique”; ie, unlabelled rabbit anti-human antibody followed by fluorescein labelled goat anti-rabbit antibody).^{40,42,49,55} Detection of ABMA indicates full therapy (see below). Independent of the diagnosis, patients with uremia or intractable heart failure must begin dialysis immediately as the starting point of their management; the clinical response to the procedure may help to differentiate pulmonary edema (clearing infiltrates) from pulmonary hemorrhage (persistent infiltrates).

Although extrarenal manifestations are common in patients with Wegener's granulomatosis, renal involvement may be the single item of initial evidence.^{19,20} The late appearance of extrarenal involvement may delay considerably the diagnosis of Wegener's granulomatosis.^{3,4,6,20,21} A kidney biopsy will show the nonspecific paucimmune vasculitis and necrotizing-crescentic glomerulonephritis.^{17-21,52,65} The lack of immunofluorescence rules out the diagnoses of IC and ABMA diseases. Granulomatous glomerulonephritis is seldom found in Wegener's syndrome,¹⁷⁻²¹ and the lung biopsy must be obtained from a typical granulomatous cavitating lesion to be specifically diagnostic.^{3,4,66,67} In the presence of the renal lesions described earlier, the finding of high titers of cytoplasmic ANCA in serum are confirmatory of Wegener's granuloma, idiopathic RPGN, and polyarteritis nodosa.⁴⁰⁻⁵⁵ Pulmonary hemorrhage in systemic lupus erythematosus (SLE) vasculitis may occur but is infrequent. In addition, positive ANA and anti-dsDNA tests and low serum complement concurrently with overt renal disease will allow separation of SLE from other diagnostic possibilities. Further confirmation and staging of the renal lesion is achieved by renal biopsy.⁵⁶

The role of both transbronchial and open lung biopsy in the diagnosis of PRS remains controversial, although it may be helpful in documenting infection. Because of the nonspecificity of lung lesions and the risks of transpleural

TABLE III. Serologic Characteristics of Immune-Mediated Conditions Producing Pulmonary Renal Syndromes

Entity	Antibasement Membrane Antibody	Immune Complexes	Anti-neutrophil Cytoplasmic Antibody	Complement (C3, C4, CH50)	Antinuclear Antibody and Anti-double Stranded DNA
Goodpasture's syndrome	+	—	—	Normal	—
Wegener's granulomatosis	—	—	+	Normal	—
			(cytoplasmic)		
Polyarteritis nodosa	—	—	+	Normal	—
			(perinuclear)		
Systemic lupus erythematosus	—	+	—	Decreased	Increased
Subacute bacterial endocarditis	—	+	—	Decreased	—
Cryoglobulinemia	—	+	—	Decreased	—
Idiopathic rapidly progressive glomerulonephritis					
Type 1	+	—	—	Normal	—
Type 2	—	+	—	Normal	—
Type 3	—	—	+	Normal	—
Type 4	—	—	—	Normal	—

* + = positive; — = negative.

procedures, lung biopsy is rarely indicated in the diagnosis of PRS.^{4,5,7,8,62-65} Moreover, with the high specificity of ANCA and ABMA determinations, it is possible that in the not too distant future, kidney and lung biopsy, particularly the latter, may be obsolete. In the words of some pulmonologists, "the value of open lung biopsy in diagnosing PRS is therefore uncertain and would seem to add little to the information provided by clinical examination and renal biopsy."⁶ Given that crescentic RPGN is common to most, if not all, cases of PRS, and that the immunopathologic expressions of IC-, ABMA-, and ANCA-mediated glomerulopathies vary widely, it will be advantageous for the clinician to classify this entity as indicated in Figure 5. The four categories of crescentic RPGN are clearly distinguishable on the basis of presence or absence of the indicated serologic markers.

ANCA bound to specific antigens are detected using indirect fluorescence techniques that incorporate successive antibodies. The first, unlabelled rabbit anti-human immunoglobulin, attaches to the patient's antibody that is already present. The second, goat anti-rabbit Ig, is labelled with fluorescein; in the following step the preparation is examined with ultraviolet light. A positive ANCA reaction, characterized by a diffuse microgranular cytoplasmic pattern (C-ANCA), is found in over 90% of patients with active and extensive Wegener's granulomatosis. Some cases of microscopic polyarteritis nodosa may also display this reaction. A predominantly perinuclear pattern (P-ANCA) produces a hazy cytoplasmic stain found often in microscopic polyarteritis and occasionally in other types of vasculitis (mixed collagen, SLE, and Kawasaki's disease).^{33,45-47,55} A quantitative radioimmunoassay (RIA), developed recently by Lockwood, Jayne

and others,^{42,54} uses a solid phase procedure, which documents that ANCA may be of the IgG and IgM isotypes. The concurrent use of both techniques, indirect immunofluorescence and RIA (or enzyme linked immunosorbent assay, ELISA), provides the most reliable methodology available today to measure ANCA. Lastly, glomerular eluates that contain IgG which binds specifically to cytoplasmic antigen(s) have been demonstrated by solid phase radioimmunoassay in Wegener's patients.⁵⁴

The sensitivity of ANCA in diagnosing Wegener's granulomatosis varies from 85% to 100% and is seemingly related to the severity of lesions. Rarely, patients in full remission have a positive reaction even at high titers; conversely, it is rare for active and generalized disease to display negative ANCA.⁵⁵ Intercurrent febrile infections may mimic reactivation of Wegener's granulomatosis; in these instances, ANCA remains negative. An increasing ANCA titer can precede true activation of disease and can remain elevated for up to eight weeks after therapy-induced remission, an important clinical observation to keep in mind in follow-up studies of patients.^{43-46,52} Moreover, ANCA becomes negative as the disease is successfully treated; on recurrence or insufficient therapy it becomes positive, often before the condition is clinically detectable. In summary, ANCA determinations fulfill a major diagnostic role, gauge the therapeutic success, and uncover early and subtle flare-ups of the disease.^{40,55,66}

TREATMENT

The information reviewed implies that strategies developed to prevent or control immune mediated and/or inflammatory processes responsible for PRS will benefit patients. Although seemingly simplistic, this highly sophisticated approach has been successfully applied in numerous clinical situations and has proven its worth in PRS. Many studies published since the late 1960s^{58,62,63,67,69-71} indicate that we possess a rather limited choice of therapies that are applicable to most cases of PRS.

Supportive management includes assisted ventilation, dialysis, hypertension and infection control, and other general measures. Specific therapy is directed at stopping the immune process, particularly antibody production, halting the progression of inflammation, and removing autoantibodies, immune complexes, and other mediators of tissue injury. These goals are frequently achieved with administration of immunosuppressive medications (cyclophosphamide, chlorambucil, cyclosporin-A), anti-inflammatory drugs (prednisone or its derivatives), and by plasmapheresis (Table III).^{6,9,17,31,66,67,69,70} Disappointing results have been reported when immunosuppressive treatment was given orally to patients with severe Goodpasture's syndrome.

If one considers ABMA disease and vasculitis-associated RPGN as a group, progression occurs, in general, in 90% of cases. Data reviewed by Bolton and Sturgill⁹ indicate that the overall prognosis of acute crescentic RPGN is poor, with 73% of patients dying or progressing to end-stage renal disease, particularly in oligoanuric individuals, despite conventional oral therapy (ie, prednisone and immunosuppressive agents). If ABMA disease is singled out, the overall mortality of RPGN drops to 63%, with

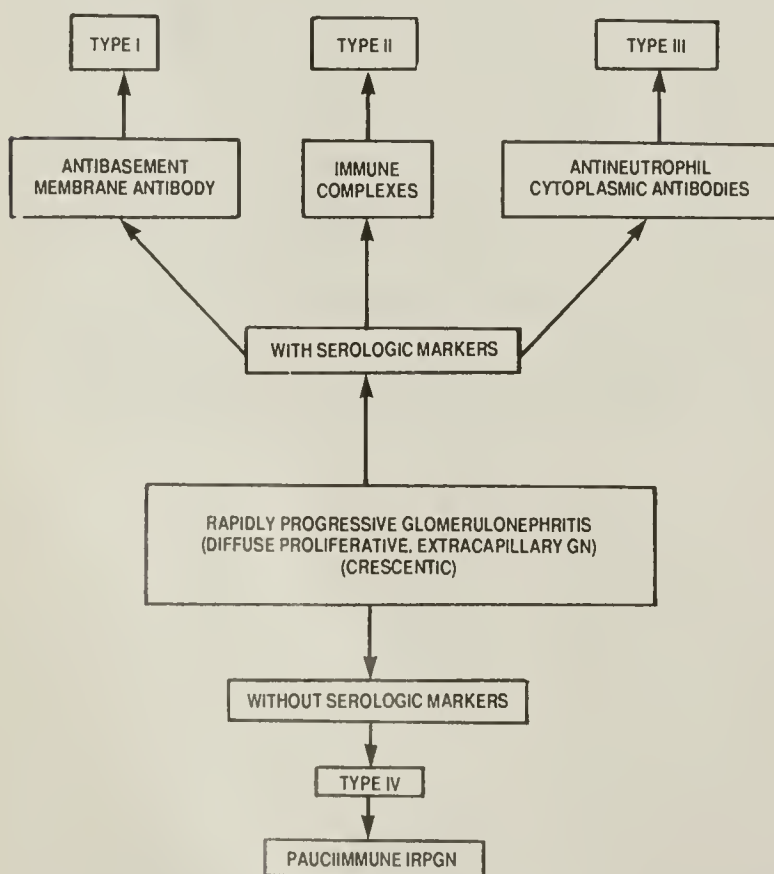


FIGURE 5. Classification of rapidly progressive glomerulonephritis based on the presence or absence of serologic markers.

improvement observed in the remaining 37%.

It is estimated that with crescentic involvement of more than 75% of glomeruli, kidney survival is dismal, a finding that correlates well with oligoanuria and serum creatinine levels greater than 6 mg/dL at presentation of PRS. These parameters are considered reliable indicators of poor prognosis in more than 90% of cases, whereas non-oliguric patients with lower creatinine do significantly better.^{13,54} On the other hand, lung hemorrhage usually responds well to therapy, independently of serum creatinine levels.^{13,54} Oliguric individuals with a severely compromised glomerular filtration rate (high creatinine) show extensive renal necrosis and crescents that comprise 85% to 100% of glomeruli; however, crescents alone do not always correlate well with poor prognosis. At present, most investigators recommend aggressive intravenous corticosteroid and cytotoxic agents with pheresis therapy only in patients with Goodpasture's syndrome who have a fair chance of recovering renal function (Tables IV, V, VI). In patients with Goodpasture's syndrome who undergo plasmapheresis, the levels of circulating ABMA decrease faster than in patients who receive drug therapy alone.⁷⁰ In addition, more stable renal function (with lower serum creatinine) on long term follow-up has been documented.⁷⁰

In all three major causes of PRS, ABMA- and ANCA-mediated diseases, and paucimmune IRPGN, triple therapy (intravenous solumedrol and cytoxan, and plasmapheresis) has made a significant impact. No therapy or immunosuppressive agents alone result in end stage renal disease in about 75% of patients with Goodpasture's syndrome; in 20% of cases, death is due to pulmonary hemorrhage.^{70,71} Occasional spontaneous remissions may occur, but the precise statistics on this are unknown. The series published by Johnson et al⁷⁰ indicates that faster disappearance of ABMA and favorable outcome, in terms of renal failure, occurred in six of eight patients given triple

therapy. Only three of nine patients treated with immunosuppressive therapy alone improved. Highly successful, prospective therapeutic trials using combined (corticosteroid-immunosuppression) oral treatment were conducted by Fauci and collaborators¹⁷ in patients with Wegener's granulomatosis.

Mean survival of untreated Wegener's is only five months, with 90% of patients dying within two years.⁷¹ Steroid therapy improves survival in Wegener's granulomatosis, increasing it to 12.5 months,⁷¹ while including cytotoxic agents yields remissions of up to 63 months.¹⁷ Bolton and Sturgill⁹ reported their experience using prednisone (daily, followed by an alternate day regimen which was subsequently tapered and discontinued) combined with cytoxan. With this regimen, in which cytoxan was maintained alone for at least one year after the initial remission, 79/85 (93%) patients with RPGN stayed in remission for a mean of 53 ± 4.3 months. Six of the 85 patients died of the disease, and four died of unrelated causes while in remission, which averaged 48.1 ± 3.6 months with a range of seven months to 13.2 years in 75 survivors. Twenty-three patients were off therapy for 35.3 ± 6.3 months (Table VII). Another recent review of the diagnosis and management of glomerulonephritis-vasculitis presenting as acute renal failure has been reported by Jennette and Falk.⁷²

It is important to remember that to start therapy of PRS, all the clinician requires, in addition to the physical diagnosis, is a demonstration of necrotizing proliferative crescentic glomerulopathy. The finding of positive fluorescence in kidney tissue and of serum ABMA and ANCA are desirable to provide diagnostic confirmation, but are not necessary to indicate intravenous immunosuppressive treatment. Conversely, symptoms and signs strongly suggestive of Wegener's granulomatosis associated with high titers of ANCA may be considered sufficient evidence to initiate immunosuppressive therapy⁶⁶ even in

TABLE IV. Suggested Specific Therapy of Pulmonary Renal Syndromes

Condition	Therapy		
	Corticosteroid	Immunosuppressive	Plasmapheresis
Goodpasture's syndrome			
Non-oliguric	Yes	Yes	Yes
Creatinine <6.0 mg/dL	IV* pulse	IV cytoxan	Daily for 10 days
Oliguric-anuric	Yes	No	No
Creatinine $\geq$ 6.0 mg/dL	IV pulse	—	—
Wegener's granulomatosis	Yes (daily-alternately or IV pulse)	Yes Cytoxan (oral or IV pulse)	Yes Daily for 10 days
IRPGN	Yes	Yes	Yes
Type 1	IV pulse, oral maintenance	IV pulse	Daily for 10 days
Type 2	IV pulse, oral maintenance	IV pulse	Daily for 10 days
Type 3	IV pulse, oral maintenance	IV pulse	Daily for 10 days
Type 4	IV pulse, oral maintenance	IV pulse	May be used
Systemic lupus erythematosus	Yes	Yes	Yes
Cryoglobulinemia	Yes	Yes	Yes
Subacute bacterial endocarditis	Yes	No	May be used
	IV pulse, oral maintenance	IV pulse	Daily for 10 days
Polyarteritis nodosa	Yes	May be used	May be used
Systemic necrotizing arteritis	IV pulse, oral maintenance	IV pulse, oral	If ANCA +

* IV = intravenous.

† Although immunosuppressive therapy may be indicated in some cases, antibiotic therapy is an indispensable adjunct in SBE.

TABLE V. Dose of Glucocorticoid and Immunosuppressive Agents in the Treatment of Pulmonary Renal Syndromes

	Oral	Intravenous
Prednisone	0.5 mg/kg/day (45–60 mg/m ² /BSA*/day)	Pulse: 5–15 (up to 30) mg/kg [†] (300–1000 mg/m ² /BSA/day)
Cytosan	0.5–2 mg/kg/day (45–60 mg/m ² /BSA/day)	Pulse: 20–25 mg/kg (500–700 mg/m ² /BSA/day; maximum 2.0 g); for glomerular filtration rate $\leq \frac{1}{3}$ normal, dose should be reduced to 4 mg/kg or 150 mg/m ² /BSA
Chlorambucil	0.2 mg/kg/day (4–8 mg/m ² /BSA/day)	
Cyclosporin-A	4–7 mg/kg/day (100–200 mg/m ² /BSA/day)	

* BSA = body surface area.

[†] As methyl prednisolone (Solumedrol).

the absence of diagnostic tissue findings (personal communication, C. M. Lockwood, 1989).

Further clinical and experimental studies would enhance our knowledge of the pathogenesis and therapeutic possibilities of these conditions. Wegener's granulomatosis, which a few years ago was uniformly fatal, is nowadays effectively controlled with the therapeutic approach described above. Not only are prolonged remissions expected but in numerous cases complete cures can be obtained. In Goodpasture's syndrome, however, the success rate is still poor and less predictable than that of Wegener's granulomatosis.

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TABLE VI. Toxic Effects of Anti-Inflammatory and Immunosuppressive Medications

Glucocorticoids	Cytosan
Growth stunting	Marrow suppression
Secondary Cushing's syndrome	Anemia
Hypercatabolism	Neutropenia
Muscle atrophy	Thrombocytopenia
Abnormal fat distribution	Highly increased susceptibility to infections
Osteoporosis	Gastrointestinal problems
Osteonecrosis	Alopecia
Hypertension	Aspermia
Skin striae	Ovarian atrophy
Cataracts	Hemorrhagic cystitis
Hyperglycemia	Lung fibrosis
Psychosis	Syndrome of inappropriate antidiuretic hormone
Polyneuropathy-lymphopenia	Lymphomas
Hyperviscosity syndrome	
Hypercoagulability syndrome	
Diabetes	
Gastrointestinal bleeding	
Susceptibility to infections	

TABLE VII. Response of Patients with Rapidly Progressive Glomerulonephritis to Conventional (Oral) and Pulse (Intravenous) Glucocorticosteroid and Immunosuppressive Therapy, 1974–1985*

Entity	Conventional Therapy [†]			Pulse Therapy		
	N	No. Improved	%	N	No. Improved	%
Vasculitis	3	0/3	0	4	4/4	100 [†]
Immune complex disease	7	1/7	14	9	7/9	78 [†]
No immune deposits	2	2/2	100	21	16/21	76 [†]
Anti-GBMA disease	5	0/5	0	12	2/12	17
Total	17	3/17	17	46	29/46	63

* Source: Reference 9.

[†] Improvement for non-AGBMA disease with conventional vs pulse therapy was 25% vs 75%, respectively.

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Administrative challenges in delivering inner city renal care

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In the mid-1970s, a group of university based Brooklyn nephrologists recognized that the borough was sorely lacking in appropriate out-of-hospital freestanding dialysis facilities to care for its ever-increasing population of patients with end stage renal disease (ESRD). To meet this service need, the renal physicians, in conjunction with several concerned citizens, established the Nephrology Foundation of Brooklyn (NFB) as a nonprofit organization dedicated to providing high quality dialysis care in a freestanding setting, while concurrently promoting and supporting educational and research activities in the field of kidney disease.¹ In December 1979 NFB opened its initial 20-station dialysis facility.

Today, NFB operates three outpatient centers in Brooklyn, and provides dialysis care for over 400 ESRD patients. Two of the centers (North Unit and East Unit) can be characterized as inner-city facilities. Patients in these centers are overwhelmingly minority (81% black, 15% Hispanic) and economically disadvantaged (71% Medicaid eligible). The third facility (South Unit) serves a racially and economically mixed, geriatric population.

Generally, NFB's patient census is not inconsistent with Brooklyn's overall racial composition which is heavily minority in the northern/central portions of the borough, and predominantly white in the southern half.² However, the ethnic composition at NFB's inner city facilities sharply contrasts with that of the dialysis population nationwide where more than 60% of the patients are white and a third are black.³ The statewide experience also mirrors the national distribution as well.⁴

ADMINISTRATIVE CONCERNS

In providing outpatient dialysis services to inner city patients with renal failure, NFB faces several administrative challenges not uncommon to other inner city health care providers, including the following.

Financial. More than 92% of US dialysis patients are Medicare eligible,⁵ while at NFB only 73% of the patients (with a range, by facility, of 69–81%) are covered by Medicare insurance.

A significant percentage of NFB's patients are Medicaid eligible. Twenty-one percent of the patients have primary Medicaid coverage, and an additional 45% have secondary Medicaid coverage. Unfortunately the timing of

payments from Medicaid can be quite erratic. Thus, treating a large number of Medicaid eligible patients means that cash flow is uneven and difficult to project. Further, since patients covered by Medicaid require periodic recertification, lapses in coverage are not uncommon. Finally, many health care providers do not accept patients with Medicaid coverage, so arranging for certain ancillary services for these patients can be problematic. In general, having a large number of Medicaid patients puts significant burdens on inner city dialysis providers from a financial as well as a service point of view.

Compliance. Life on maintenance hemodialysis is quite challenging even for the most structured individual. Patients must adhere to strict dietary guidelines, severely restrict their fluid intake, medicate themselves several times a day, and travel to a dialysis center three times a week. Many middle class patients have trouble following the therapeutic restrictions. Not surprisingly, patients from economically disadvantaged backgrounds, who in many instances live in substandard housing without the benefit of adequate family support systems, have a great deal of difficulty complying with the complex hemodialysis regime. Fluid overload, inconsistent adherence to self-administration of medication doses, dangerously abnormal laboratory values, and missed dialysis treatments are all consequences of this behavior pattern which leads to harder-than-average patient management problems.

The aforementioned clinical situations can also be viewed as economic problems as well. From the facility's standpoint, missed treatments result in extra costs (eg, scheduled staff) without any corresponding revenue. From the health care system viewpoint, noncompliant patients tend to become sicker more frequently, to utilize more emergency room services, and to have higher hospitalization rates. The problem then comes around full circle, as higher hospitalization rates mean more vacant slots in the outpatient dialysis facility and thus less revenue. Compliance with the dialysis regime, then, can have major financial implications for the inner city dialysis facility, in addition to its well-recognized clinical complications for the patient.

Security and Crime. Criminal violence in health facilities has increased and has become much more serious in nature during the 1980s, with most indicators showing that the number and severity of such incidents will increase even more during the next decade.⁶ In 1989, for example, at Kings County Hospital Center in Brooklyn (one of NFB's primary referring institutions), hospital police responded to 6,965 calls for assistance and made 122

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arrests, 95 of which were for felonies.⁷ In a Bronx dialysis facility several years ago a nephrologist was shot by one of his patients. At NFB, staff have been assaulted, threatened, and verbally abused by patients. Staff have been mugged on their way to work, and NFB facilities have been burglarized. On one such occasion, the burglar entered through the narrow duct of a rooftop heating/ventilating/air conditioning (HVAC) system of a nearly impregnable building. Further illustrating the ambience, NFB was fined for a "false alarm," while thieves were making away with several patient television sets. Crime prevention programs in the form of buzzer systems, intercoms, closed-circuit television cameras, razor-wire, and security guards, to one degree or another, have all become part of the necessary routine at our inner-city dialysis centers. These crime prevention efforts drive up the cost of providing services in this setting, and have a significant, though unquantified, psychological impact on caregivers and law-abiding patients alike.

Staff Recruitment and Retention. In an era of shortages of qualified health care personnel, abusive patients with higher than average rates of AIDS and substance abuse present significant obstacles to staff recruitment and retention. It requires a dedicated staff to work in such an environment and it is an even greater challenge to find and retain such individuals.

PLANNING THE SYMPOSIUM

At the end of 1989, as NFB was about to celebrate its tenth anniversary, Dr Eli Friedman approached the foundation's board with a request to sponsor a symposium on inner city nephrology. The objective of the program would be to inform health care professionals of the unique clinical problems associated with inner city patients afflicted with kidney disease, and the difficulties encountered in treating such patients. Months earlier, Clive O. Callender, MD, had discussed "Renal Disease in African-Americans" at the 25th anniversary celebration of the State University of New York Health Science Center at Brooklyn's renal dialysis program. The intention was to build on Dr Callender's presentation and organize a com-

prehensive teaching day dedicated to exploring the myriad of clinical complications associated with inner city nephrology, including hypertension, diabetes, AIDS, substance abuse, etc. The NFB board was well aware of the problems the foundation itself faced on a day-to-day basis in providing care to its inner city patients. Based on its desire to support educational programs in the field of kidney disease, and given the demographic characteristics of its patients, the NFB board heartily endorsed the symposium proposal and authorized support to organize the event. As evidenced by the articles in this issue, the symposium generated a provocative and timely series of presentations with relevance to all inner city nephrology caregivers.

CONCLUSION

Organizing services for ESRD patients is a complex task under any circumstances. The inner city dialysis provider is also faced with many other factors that make the job even more demanding. Maintaining fiscal solvency, ensuring patient compliance with the dialysis regimen, coping with an increased risk of personal and property crime, recruiting and retaining staff, and sustaining morale when faced with antisocial patient behavior are everyday issues that become exacerbated in the inner city setting. I salute the thousands of ESRD caregivers who day in and day out dedicate their careers to serving and treating the neediest of our dialysis patients.

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Epidemiology of developmental disabilities in the City of Albany, New York

The New York State Department of Health (NYS-DOH) Disability Prevention Program, funded by a grant from the US Centers for Disease Control, works to improve the surveillance of disabilities. To date, most studies of the incidence of developmental disabilities have relied on data obtained from screening programs that, by their very nature, may be unrepresentative samples of the entire at-risk population. What is often lacking are data on incidence and risk factors associated with developmental disabilities from a population-based study. Population-based surveillance is necessary to document the extent of developmental disabilities in New York State. It is also necessary to develop baseline measures against which the effectiveness of preventive interventions can be evaluated. For developmental disabilities, the challenge is to use multiple agency data sets to arrive at unduplicated estimates of the incidence of developmental disabilities.

The Albany Developmental Disabilities Project represents an initial effort to fill these gaps by providing data on a representative sample of children born in 1985 to mothers resident in the city of Albany, New York. It provides data on population-based incidence as well as information on methodologic parameters needed to apply the findings to a larger system.

The project combines data from two mutually exclusive screening programs operating in Albany, along with linkage to birth record files, to provide a common set of variables. One of the screening programs used is the statewide Infant Health Assessment Program (IHAP). IHAP screens children characterized as high-risk for developmental disability and/or physical growth retardation. Selection of high-risk individuals for inclusion in IHAP is made on the basis of low birthweight, low maternal age, low gestational age and other indices. The Pre-School Early Development Screening Program (PEDS) provides the opportunity for screening to all remaining children born to mothers residing in the City of Albany who have not been screened through the IHAP program. Data from these two mutually exclusive programs for children born in 1985 were combined and linked to birth record files. Developmental disability was assessed using standard methods based on Gesell developmental screening test scores that classify children into one of three categories: Normal, Suspect, or Abnormal.¹

A sample of 520 children out of a possible 1,532 chil-

dren born in 1985 to mothers resident in Albany was selected from the combined IHAP/PEDS database. Comparisons of the IHAP/PEDS sample with the total population of children born to Albany resident mothers were made based on child's sex, birthweight and gestational age; maternal and paternal age, education, and race; and mother's reproductive history. Of these comparisons, only mother's education showed a significant difference ($p < 0.05$) between the sample and the overall population, indicating that the sample is fairly representative of the entire birth cohort.

Of the 520 children in the IHAP/PEDS sample, 440 (84.6%) were classified as "Normal," 59 (11.3%) were classified as "Suspect," and 21 (4.0%) were classified as "Abnormal." Statistical tests were performed to detect differences between the two extreme groups, "Normal" and "Abnormal," excluding those classified as "Suspect." There were no significant associations ($p > 0.05$) between developmental status and sex of the child, gestational age, Apgar scores, number of prenatal visits, month that prenatal care began, number of previous pregnancies, maternal education, parental age, parental race or the presence of complications during labor or pregnancy. Fathers who completed high school had a significantly lower percentage of abnormal children (2.9%) than fathers who did not complete high school (11.1%). This suggests some influence of socioeconomic status. Women with a previous history of spontaneous abortion had a significantly lower percentage of abnormal children (0%) than women who had never had a spontaneous abortion (5.6%). The most striking statistical difference between "Normal" and "Abnormal" children in the IHAP/PEDS sample is birthweight; the mean birthweight of "Abnormal" children is 2,968 grams compared to a mean birthweight of 3,353 grams for "Normal" children. Closer examination shows that those children most at risk of developmental delay are those with birthweights between 2,000 and 2,500 grams. Children with birthweight less than 2,000 grams or greater than 2,500 grams are not at greater risk of developmental disability. The low risk associated with very low birthweight babies may be due to a selection process; very low birthweight babies are less likely to survive, and those that do are usually fairly healthy.

While the sample size in this project is relatively small, the results are consistent with what is known about the epidemiology of developmental disabilities. In addition, the lessons learned about linkage from diverse sources of data covering an entire geographic area may have wider applicability in the future.

References

1. Knobloch H, Stevens F, Malone AF: *Manual of Developmental Diagnosis*. Hagerstown, Md, Harper and Row, 1980.

Bicycle safety update

This information supplements the article in the April

1990 issue of *Epidemiology Notes* on bicycle injuries and efforts to prevent or reduce the number and severity of these injuries.

Driving a bike during twilight or at night can be dangerous. Retro-reflective cloth sewn on a jacket, reflective dots on the back of shoes and other reflectors will increase visibility of cyclists and help to prevent bicycle injuries, especially those involving collision with a motor vehicle. The NYS Vehicle and Traffic Law, Section 1236, Part (a), requires that every bicycle in use during the period one half hour after sunset to one half hour before sunrise must be equipped with a lamp on the front which emits white light during the hours of darkness from a distance of at least 500 feet to the front. In addition, a red light must be visible to the rear for a distance of 300 feet. At least one of these required lights must also be visible for 200 feet from each side.

For more information, contact the Injury Control Program, New York State Department of Health, Empire State Plaza, Corning Tower Room 621, Albany, NY 12237, (518) 473-1143.

County Data Book

The New York State Department of Health has recent-

ly published a County Data Book in an effort to assist county governments and local providers in assessing their public health needs and priorities.

The publication presents county-specific information on measures of mortality, morbidity and natality such as infant, neonatal and postneonatal mortality rates, incidence of selected diseases, cancer incidence, communicable disease rates, pregnancy rates and rates of low birth-weight and premature births. In addition, the publication contains information on local services such as the supplemental income for Women, Infants and Children (WIC) Program, prenatal care and home health services. The book also presents socioeconomic indicators such as civilian employment rates.

Where appropriate, time trends, county maps and comparisons with the US Surgeon General's goals for the year 2000 are presented.

The data book will be adapted from year to year to further assist local health officials and providers of health services.

Single copies of the New York State County Data Book may be obtained from the New York State Department of Health, Office of Public Health Management, Corning Tower, Room 750, Empire State Plaza, Albany, NY 12237 or by calling (518) 474-2543.

Short-time dialysis is associated with increased mortality

The duration of dialysis is a key element in assessing the effectiveness of the procedure. The results of a three-year study (1984–1987) of approximately 600 patients in 36 dialysis facilities nationwide, examining patient outcomes and mortality by duration of dialysis procedures, found increased mortality with shortened dialysis time (*JAMA* 1991; 265:871–875).

Short-time dialysis, defined as averaging less than three hours and 30 minutes, was represented by 20% of the patients, long-time dialysis, averaging at least four hours and 15 minutes, by 6% of the patients, and conventional-length dialysis, averaging four hours of dialysis per session, by 74% of the patients.

The authors reported a statistically significant increased mortality risk among the short-time dialysis group compared to the conventional-length dialysis group, this risk increased with the number of years a patient had been receiving dialysis. Long-time dialysis was associated with reduced mortality compared to conventional-length dialysis, although this finding was not statistically significant.

A comparison of dialysis duration with average blood urea nitrogen (BUN) concentrations yielded no statistically significant differences between the patient groups. The short-time dialysis patients had an 8% ($p < 0.01$) lower average hemoglobin level than the conventional-length dialysis group, suggesting "inadequate dialysis in the short-time dialysis group."

The authors note that at the time of this study, the clearance capacity of dialysis units was not comparable to some of the models available today. "In the current era of high-flux, high-efficiency dialysis, when dialysis times are being considerably shortened while still providing Kt/Vs of greater than 1, the major conclusion to be drawn from this article is that an arbitrary prescription using BUN level as the relevant indicator may not recognize the adverse combination of underdialysis and undernutrition."

Is partial nephrectomy a viable alternative for renal cell carcinoma?

To lessen the risk of metastasis, and because a person can live with one healthy kidney, the preferred treatment for localized renal cell carcinoma is radical nephrectomy. Partial nephrectomy is often the treatment of choice for renal cell carcinoma in patients with bilateral tumors, with tumor in the sole kidney, and with a diseased contralateral kidney. Provet et al reviewed their experience with partial nephrectomy to assess the incidence of local recurrence and metastases, as well as patient survival, with a conservative approach to surgery (*J Urol* 1991; 145:472–476).

The authors focused on the records of 44 patients who underwent 50 partial nephrectomies at New York University Hospital between 1974 and 1988. All of the tumors were peripherally located; the mean diameter was 2.6 cm.

Removal of the tumor under hypothermia included excision of a "1 to 2 cm. rim of normal parenchyma at the margins of the lesion," in an effort to reduce the risk of local recurrence.

The mean follow-up period was 36 months. Sixteen patients underwent mandatory partial nephrectomy; one died of renal failure; three died of recurrent local or metastatic carcinoma; 12 patients were alive at last follow-up—11 had had no recurrence. Twenty-seven of the 28 patients who underwent elective partial nephrectomy were alive at last follow-up; none experienced local ipsilateral or metastatic disease. One patient died of unrelated medical complications.

The advent of improved imaging techniques has led to earlier and incidental discovery of smaller renal tumors, which may be amenable to treatment with partial nephrectomy. Additional studies with longer follow-up periods may support this more conservative approach.

Use of the emergency room observation unit to treat acute pyelonephritis

Patients with acute pyelonephritis require antibiotic therapy and must often be admitted to the hospital for intravenous antibiotics and supportive care. Whereas outpatient management of pyelonephritis has shown some promise in mildly ill patients, Israel et al evaluated the outcome of moderately to severely ill patients who were treated for acute pyelonephritis in an emergency department observation unit (*Ann Emerg Med* 1991; 20:253–257).

The maximum time for treatment in the observation unit was 12 hours, after which patients were either discharged home on outpatient treatment or admitted to the hospital. In general, therapy included ampicillin, followed by discharge on oral amoxicillin, or in cases of penicillin allergy, therapy with trimethoprim/sulfamethoxazole in the observation unit and continued on discharge. Improvement in symptoms and the ability to maintain oral fluids and antibiotics were conditions for discharge.

Of the 147 patients included in this study, 87 with pyelonephritis had documented follow-up. Sixty-three (72%) were treated solely in the observation unit and were asymptomatic at follow-up. Nineteen (22%) were admitted to the hospital after treatment in the observation unit for reasons of intractable pain and/or vomiting. Five patients (6%) were discharged home, but returned to the emergency department. "In our study, no clinical or laboratory variable could predict the outcome of ED observation unit and outpatient therapy." Significant missed diagnoses included pelvic inflammatory disease, ruptured appendix, hepatitis, and nephrolithiasis.

The authors note the absence of long term data with outpatient therapy, and the possibility that "inadequate treatment of acute pyelonephritis may on occasion lead to chronic renal damage." They emphasize the need for close outpatient follow-up to ensure microbiologic cure and relief of symptoms.

OBITUARY LISTINGS

Sidney Aiken, MD, Massena. Died December 12, 1990; age 86. Dr Aiken was a 1929 graduate of the University of Toronto, Faculty of Medicine, Toronto, Canada. He was a member of the Medical Society of the County of St Lawrence and the Medical Society of the State of New York.

J. Edwin Alford, MD, Buffalo. Died November 6, 1990; age 81. Dr Alford was a 1934 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Fellow of the American College of Surgeons, a Diplomate of the American Board of Surgery, and a Diplomate of the American Board of Colon and Rectal Surgery. His memberships included the New York Academy of Medicine, the American Society of Colon and Rectal Surgeons, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Bernard Amsterdam, MD, New York. Died January 7, 1991; age 86. Dr Amsterdam was a 1930 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Diplomate of the American Board of Internal Medicine. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Barbara Grime Batcheller, MD, Phelps. Died January 24, 1991; age 68. Dr Batcheller was a 1948 recipient of the Registrable Qualification Granted by the English Conjoint Board. She was a Diplomate of the American Board of Anesthesiology. Her memberships included the New York State Society of Anesthesiologists, the Ontario County Medical Society, and the Medical Society of the State of New York.

Biagio Battaglia, MD, Brooklyn. Died January 14, 1991; age 81. Dr Battaglia was a 1933 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians, and a Fellow of the American College of Chest Physicians. He was a member of the American Thoracic Society, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Philip Bond, MD, Port Washington. Died January 14, 1991; age 81. Dr Bond was a 1934 graduate of Medizinische Fakultät der Universität Heidelberg, Heidelberg, Baden-Württemberg, Germany. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

George Lewis Camillery, MD, Newark. Died October 13, 1990; age 45. Dr Camillery was a 1972 graduate of New York Medical College. He was a Diplomate of the American Academy of Family Practice and a Fellow of the American Academy of Pediatrics. He was a member of the Medical Society of the County of Wayne and the Medical Society of the State of New York.

Thomas Ciaccio Case, MD, New York. Died January 1, 1991; age 87. Dr Case was a 1926 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Surgery, a Fellow of the American College of Surgeons, and a Qualified Fellow of the International College of Surgeons. He was a member of the New York Academy of Medicine, the American Geriatrics Society, the New York County Medical Society, and the Medical Society of the State of New York.

Alan I. Chalfin, MD, Long Beach. Died January 15, 1991; age 50. Dr Chalfin was a 1967 graduate of Medizinische Fakultät, Universität Basel, Basel, Switzerland. He was a Diplomate of the American Board of Ophthalmology and a Fellow of the American College of Surgeons. His memberships included the New York Ophthalmology Society, the American Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology, the Nassau County Medical Society, and the Medical Society of the State of New York.

William Colomba Clyne, MD, Bronx. Died February 6, 1991; age 82. Dr Colomba was a 1932 graduate of the National University of Ireland. He was a Fellow of the American College of Chest Physicians. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

John E. Connelly, MD, Albany. Died

November 25, 1990; age 67. Dr Connelly was a 1952 graduate of the Albany Medical College. He was a member of the Medical Society of the County of Albany and the Medical Society of the State of New York.

Philip Crastnopol, MD, Floral Park. Died February 6, 1991; age 73. Dr Crastnopol was a Diplomate of the American Board of Surgery, a Diplomate of the American Board of Thoracic Surgery, and a Fellow of the American College of Surgeons. He was a member of the American Association for Thoracic Surgery, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Aaron Dolinsky, MD, White Plains. Died December 29, 1990; age 64. Dr Dolinsky was a 1953 graduate of the Medical College of Georgia, School of Medicine, Augusta, Georgia. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the New York Academy of Medicine, the American Psychiatric Association, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Rodney H. Dusenberre, MD, Ithaca. Died February 7, 1991; age 68. Dr Dusenberre was a 1947 graduate of the Cornell University Medical College. He was a Diplomate of the American Board of Surgery and a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Tompkins and the Medical Society of the State of New York.

Howard Gabriel Ehrlich, MD, New York. Died November 25, 1990; age 60. Dr Ehrlich was a 1955 graduate of Tulane University School of Medicine, New Orleans, Louisiana. He was a member of the American Society of Internal Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

Walter Einhorn, MD, Purchase. Died February 2, 1991; age 83. Dr Einhorn was a 1932 graduate of the Universität Wien, Medizinische Fakultät, Wien, Austria. He was a Diplomate of the American Board of Family Practice and a Fellow of the American Academy

of Family Physicians. He was a member of the New York Cardiological Society, the American Geriatrics Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

Rudolf J. Elsberg, MD, Elmhurst. Died August 20, 1990; age 81. Dr Elsberg was a 1937 graduate of the Facolta di Medicina e Chirurgia, Universita di Bologna, Bologna, Italy. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Sigmund Erber, MD, Brooklyn. Died February 3, 1991; age 83. Dr Erber was a 1931 graduate of Universitaet Wien, Medizinische Fakultät, Wien, Austria. He was a Fellow of the American College of Angiology. He was a member of the American Geriatrics Society, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Benedict Victor Favata, MD, Los Angeles, California. Died January 10, 1991; age 81. Dr Favata was a 1942 graduate of the University of Rochester School of Medicine and Dentistry. He was a member of the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Stuart Forster, MD, New York. Died January 11, 1991; age 44. Dr Forster was a 1975 graduate of the Albert Einstein College of Medicine of Yeshiva University, Bronx. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Mukesh N. Gatha, MD, East Islip. Died December 28, 1990; age 40. Dr Gatha was a 1972 graduate of B.J. Medical College, Gujarat University, Ahmedabad, Gujarat, India. He was a Diplomate of the American Board of Anesthesiology. His memberships included the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, Inc, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Joseph Raymond Giunta, MD, Olean. Died November 4, 1990; age 85. Dr Giunta was a 1933 graduate of Georgetown University School of Medicine, Washington, DC. He was a member of the American Geriatrics Society, the

Medical Society of the County of Cattaraugus, and the Medical Society of the State of New York.

Burt Anthony Glass, MD, Whitestone. Died February 2, 1991; age 78. Dr Glass was a 1937 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Diplomate of the American Board of Family Practice and a Fellow of the American College of Family Physicians. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Brij Gopal Goel, MD, Schenectady. Died July 15, 1990; age 51. Dr Goel was a 1962 graduate of King George's Medical College, Lucknow University, Lucknow, Uttar Pradesh, India. He was a Fellow of the American College of Cardiology, a Fellow of the American College of Chest Physicians, and a Fellow of the American College of Angiology. His memberships included the New York State Society of Internal Medicine, the New York Cardiological Society, the Medical Society of the County of Schenectady, and the Medical Society of the State of New York.

Isidor Goldberg, MD, Bronx. Died November 18, 1990; age 94. Dr Goldberg was a 1924 graduate of the New York University School of Medicine. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Lazari Goldmann, MD, Suffern. Died December 17, 1990; age 82. Dr Goldmann was a 1932 graduate of the Universitaet Wien, Medizinische Fakultät, Wien, Austria. He was a Fellow of the American College of Angiology. He was a member of the Medical Society of the County of Rockland and the Medical Society of the State of New York.

Albert Carlos Hoheb, MD, Loudonville. Died November 24, 1990; age 65. Dr Hoheb was a 1959 graduate of the Facolta di Medicina e Chirurgia, Universita di Bologna, Bologna, Italy. He was a Diplomate of the American Board of Pathology. He was a member of the American Society of Clinical Pathologists, Medical Society of the County of Albany, and the Medical Society of the State of New York.

Jerzy Horecki, MD, Queens Village. Died November 1, 1989; age 79. Dr Horecki was a 1938 graduate of the

Universitaet Graz, Medizinische Fakultät, Graz, Austria. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Julius Kavee, MD, New York. Died April 8, 1990; age 91. Dr Kavee was a 1924 graduate of the New York University School of Medicine. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. He was a member of the American Thoracic Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

Lloyd H. Kest, MD, Great Neck. Died January 31, 1991; age 81. Dr Kest was a 1936 graduate of Georgetown University School of Medicine. He was a Diplomate of the American Board of Dermatology, Inc. His memberships included the New York Academy of Medicine, the New York State Dermatological Society, the American Academy of Dermatology, the Dutchess County Medical Society, and the Medical Society of the State of New York.

Alfred Klein, MD, Bal Harbour, Florida. Died October 14, 1990; age 91. Dr Klein was a 1924 graduate of Universitaet Wien, Medizinische Fakultät, Wien, Austria. He was a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Harold Klein, MD, Brooklyn. Died February 13, 1991; age 80. Dr Klein was a 1937 recipient of the Registrable Qualification Granted by Scottish Conjoint Board. He was a Diplomate of the American Board of Pediatrics, a Fellow of the American Academy of Pediatrics, and a Fellow of the American Psychiatric Association. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Michael D. Kraska, MD, Buffalo. Died February 16, 1991; age 84. Dr Kraska was a 1934 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Jack Lehman, MD, Elmhurst. Died January 30, 1991; age 69. Dr Lehman was a 1945 graduate of Tulane University School of Medicine, New Orleans, Louisiana. He was a Diplomate of the American Board of Radiology and a Diplomate of the American Board of Nuclear Medicine. His memberships included the New York Roentgen Society, the Radiological Society of New York State, the Radiological Society of North America, Inc, the Society of Nuclear Medicine, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

William Henry Le Strange, MD, New Hyde Park. Died May 14, 1990; age 93. Dr Le Strange was a 1925 graduate of Boston University School of Medicine. He was a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Stanley Lesse, MD, New York. Died December 20, 1990; age 68. Dr Lesse was a 1945 graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the New York Academy of Medicine, the New York Neurological Society, the Association for Research in Nervous and Mental Disease, the American Psychiatric Association, the American Academy of Neurology, the Association for the Advancement of Psychotherapy, the New York County Medical Society, and the Medical Society of the State of New York.

Marvin David Linick, MD, Chester. Died January 20, 1991; age 79. Dr Linick was a 1934 graduate of New York University School of Medicine. His memberships included the Clinical Society, the New York Diabetes Association, the American Geriatrics Society, the New York County Medical Society, and the Medical Society of the State of New York.

Paula M. Sanchez Lopez, MD, West Seneca. Died December 7, 1990; age 53. Dr Lopez was a 1961 graduate of the University of Puerto Rico School of Medicine, San Juan, Puerto Rico. She was a member of the American Psychiatric Association, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Gerald J. Lustig, MD, Staten Island. Died February 11, 1991; age 70. Dr Lustig was a 1948 graduate of the University of Colorado School of Medicine, Denver. He was a Diplomate of the American Board of Surgery, a Diplomate of the American Board of Thoracic Surgery, and a Fellow of the American College of Surgeons. His memberships included the New York Society for Thoracic Surgery, the New York State Surgical Society, the Society of Thoracic Surgery, the Richmond County Medical Society, and the Medical Society of the State of New York.

Walter B. Macomber, MD, Albany. Died February 2, 1991; age 85. Dr Macomber was a 1931 graduate of Albany Medical College. He was a Diplomate of the American Board of Plastic Surgery and a Fellow of the American College of Surgeons. His memberships included the American Society of Plastic & Reconstructive Surgery, the American Association of Plastic Surgeons, the American Surgical Association, the Medical Society of the County of Albany, and the Medical Society of the State of New York.

Leslie Stewart Massad, MD, Syracuse. Died October 1, 1990; age 57. Dr Massad was a 1958 graduate of the University of Rochester School of Medicine and Dentistry. He was a Diplomate of the American Board of Obstetrics and Gynecology and a Fellow of the American College of Obstetricians and Gynecologists. He was a member of the American Fertility Society, the Onondaga County Medical Society, and the Medical Society of the State of New York.

Alfred Metellus, MD, Hollis. Died November 6, 1990; age 60. Dr Metellus was a 1954 graduate of Ecole de Medecine et de Pharmacie, Universite d'Etat d'Haiti, Port au Prince, Haiti. He was a Diplomate of the American Board of Surgery. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Ernest Michaelson, MD, Warren, Vermont. Died January 13, 1991; age 76. Dr Michaelson was a 1938 graduate of the University of Maryland School of Medicine, Baltimore, Maryland. He was a member of the American Association of Obstetricians & Gynecologists, the Nassau County Medical Society, and the Medical Society of the State of New York.

William Henry Moore, MD, Saratoga Springs. Died December 1, 1990; age 79. Dr Moore was a 1937 graduate of Georgetown University School of Medicine, Washington, DC. He was a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Saratoga and the Medical Society of the State of New York.

Dante James Morgana, MD, Akron. Died January 4, 1991; age 94. Dr Morgana was a 1921 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Sciences, Buffalo. He was a Diplomate of the American Board of Ophthalmology, a Fellow of the American College of Surgeons, and a Qualified Fellow of the International College of Surgeons. His memberships included the New York Academy of Medicine, the American Academy of Ophthalmology and Otolaryngology, the Pan American Association of Ophthalmology, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

I. Irving Moubert, MD, Plantation, Florida. Died December 11, 1990; age 85. Dr Moubert was a 1934 graduate of the Medizinische Fakultät der Universität Heidelberg, Heidelberg, Baden-Württemberg, Germany. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Norbert Neumann, MD, Jericho. Died January 1, 1991; age 78. Dr Neumann was a 1936 graduate of the Universität Wien, Medizinische Fakultät, Wien, Austria. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Richard B. Nolan, MD, New York. Died January 14, 1991; age 69. Dr Nolan was a 1945 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Surgery, a Diplomate of the American Board of Thoracic Surgery, and a Fellow of the American College of Surgeons. His memberships included the New York Society for Cardiovascular Surgery, the New York Society for Thoracic Surgery, the New York State Surgical Society, the New York County Medical Society, and the Medical Society of the State of New York.

I. Clayton Oestreicher, MD, Cambridge.

Died August 30, 1990; age 84. Dr Oestreicher was a 1933 recipient of the Registrable Qualification Granted by Scottish Conjoint Board, Scotland. He was a member of the Medical Society of the County of Washington and the Medical Society of the State of New York.

Hugo R. Paganelli, MD, New York. Died December 9, 1990; age 84. Dr Paganelli was a 1930 graduate of George Washington University School of Medicine and Health Science, Washington, DC. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Bienvenido L. Reyes, MD, Rochester. Died January 17, 1991; age 63. Dr Reyes was a 1963 graduate of the Faculty of Medicine and Surgery, University of Santo Tomas, Manila, Philippines. He was a member of the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Joseph John Ricotta, MD, Buffalo. Died November 8, 1990; age 71. Dr Ricotta was a 1943 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science, Buffalo. He was a Diplomate of the American Board of Obstetrics and Gynecology, a Diplomate of the American Board of Surgery, and a Fellow of the American College of Obstetricians and Gynecology. His memberships included the American Fertility Society, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Anthony V. Runfola, MD, Orchard Park. Died November 13, 1990; age 79. Dr Runfola was a 1937 graduate of the Medical College of Wisconsin, Milwaukee, Wisconsin. He was a member of the American Academy of Dermatology, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Harold N. Runsdorf, MD, Brooklyn. Died January 23, 1991; age 82. Dr Runsdorf was a 1932 graduate of the Faculty of Medicine, University of Edinburgh, Edinburgh, Scotland. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Rashmikanth P. Sangani, MD, Pittsford. Died January 29, 1991; age 53. Dr San-

gani was a 1962 graduate of the B.J. Medical College, Gujarat University, Ahmedabad, Gujarat, India. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychiatric Association, the American Society of Addiction Medicine, the Medical Society of the County of Monroe, and the Medical Society of the State of New York.

Alfredo Santillo, MD, Staten Island. Died December 27, 1990; age 79. Dr Santillo was a 1937 graduate of Facoltà di Medicina e Chirurgia, Università di Parma, Parma, Italy. He was a member of the Richmond County Medical Society and the Medical Society of the State of New York.

Isadore Schlamowitz, MD, New York. Died January 5, 1991; age 75. Dr Schlamowitz was a 1940 graduate of the New York University School of Medicine. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians, a Fellow of the American College of Gastroenterology, a Fellow of the American College of Cardiology, a Fellow of the American College of Chest Physicians, and a Fellow of the American College of Angiology. He was a member of the New York Academy of Medicine, the New York Academy of Gastroenterology, the American Academy of Compensation Medicine, Inc, the American Geriatrics Society, the New York County Medical Society, and the Medical Society of the State of New York.

Eric Stamm, MD, Ferndale. Died February 6, 1991; age 82. Dr Stamm was a 1936 graduate of the Universitaet Wien, Medizinische Fakultät, Wien, Austria. He was a Fellow of the American Academy of Family Physicians. He was a member of the Sullivan County Medical Society and the Medical Society of the State of New York.

Karel Steinbach, MD, Jackson Heights. Died December 31, 1990; age 96. Dr Steinbach was a 1920 graduate of Univerzita Kardlova, Fakulta of Ped., Praha, Czechoslovakia. He was a member of the American Academy of Family Physicians, the New York County Medical Society, and the Medical Society of the State of New York.

Arthur M. Suffin, MD, Hempstead. Died January 31, 1991; age 82. Dr Suffin was a 1934 graduate of Creighton

University School of Medicine, Omaha, Nebraska. He was a Diplomate of the American Board of Anesthesiology and a Fellow of the American College of Anesthesiologists. He was a member of the American Society of Anesthesiologists, Inc, the Nassau County Medical Society, and the Medical Society of the State of New York.

Samuel Switkes, MD, Delray Beach, Florida. Died November 7, 1990; age 71. Dr Switkes was a 1944 graduate of Middlesex University School of Medicine, Waltham, Massachusetts. He was a Fellow of the American College of Anesthesiologists. His memberships included the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, Inc, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Constantin V. Teodoru, MD, Jackson Heights. Died January 18, 1991; age 76. Dr Teodoru was a 1939 graduate of the Institutul de Medicina si Farmacie, Bucuresti, Romania. He was a Fellow of the American College of Physicians. His memberships included the New York Academy of Medicine, the Endocrine Society, the American Rheumatism Association, the American Physiological Society, the Society for Experimental Biology and Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

Joseph Edward Terris, MD, Old Westbury. Died December 22, 1990; age 75. Dr Terris was a 1940 graduate of New York University School of Medicine. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Joseph Tymochko, MD, Penfield. Died January 1, 1991; age 79. Dr Tymochko was a 1938 graduate of the Akademia Medyczna Wydział Lekarski, Poznan, Poland. He was a member of the American Psychiatric Association, the Medical Society of the County of Monroe, and the Medical Society of the State of New York.

Walter S. Walls, MD, Charlottesville, Virginia. Died February 15, 1991; age 85. Dr Walls was a 1931 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Diplomate of the American Board of Surgery and

a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Erie and the Medical Society of the State of New York.

Herbert Wanderman, MD, Bethpage. Died January 17, 1991; age 69. Dr Wanderman was a 1945 graduate of the New York Medical College. He was a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Obstetricians and Gynecologist, and a Fellow of the American College of Surgeons. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Morgan J. Weber, MD, Mount Sinai. Died October 12, 1990; age 79. Dr Weber was a 1938 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Karl N. Wechtel, MD, Hewlett. Died February 12, 1991; age 86. Dr Wechtel was a 1931 graduate of Columbia University College of Physicians and Surgeons. He was a member of the New York State Society of Internal Medicine, the Nassau County Medical Society, and the Medical Society of the State of New York.

Abner I. Weisman, MD, New York. Died December 24, 1990; age 84. Dr Weisman was a 1932 graduate of New York Medical College. He was a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Surgeons, and a Fellow of the American College of Obstetricians and Gynecologists. His memberships included the New York Academy of Medicine, the American Fertility Society, the Endocrine Society, the New York County Medical Society, and the Medical Society of the State of New York.

Walter D. Westinghouse, MD, East Aurora. Died December 3, 1990; age 87. Dr Westinghouse was a 1931 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. He was a member of the New York State Society of Internal Medicine, the New York Academy of Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

William Winner, MD, Bronx. Died December 14, 1990; age 66. Dr Winner was a 1956 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Obstetrics and Gy-

necology and a Fellow of the American College of Obstetricians and Gynecologists. He was a member of the American Fertility Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

Sigmund P. Winter, MD, Santa Monica, California. Died September 3, 1990; age 90. Dr Winter was a 1925 graduate of the Univerzita Karsldova, Fakulta of Ped. Praha, Czechoslovakia. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Zofia Wojcik, MD, Forest Hills. Died October 6, 1990; age 73. Dr Wojcik was a 1949 graduate of the Akademia Medyczna Wydzial Lekarski, Warsaw, Poland. She was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Daniel I. Yale, MD, Ithaca. Died February 9, 1991; age 62. Dr Yale was a 1954 graduate of the State University of New York Health Science Center at Syracuse, College of Medicine. He was a Diplomate of the American Board of Orthopedic Surgery. He was a member of the American Academy of Orthopaedic Surgeons, the Medical Society of the County of Tompkins, and the Medical Society of the State of New York.



Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media, and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1988; 88:456-462). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal's* particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 3,000 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 1,000 and 1,500 words. Other kinds of original essays should not exceed 2,500 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with *Système Internationale* (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith² reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear in the text. When there are three or fewer authors, all should be listed; where there are four or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Bowen J: Autoimmune paraneoplastic diseases of the nervous system. *NY State J Med* 1991; 91:2-3.
2. Cotran RS, Kumar V, Robbins SL: *Robbins Pathologic Basis of Disease*, ed 4. Philadelphia, WB Saunders Co, 1989, pp 842-845.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Pascal James Imperato, MD, Editor, *New York State Journal of Medicine*, PO Box 5404, Lake Success, NY 11042.

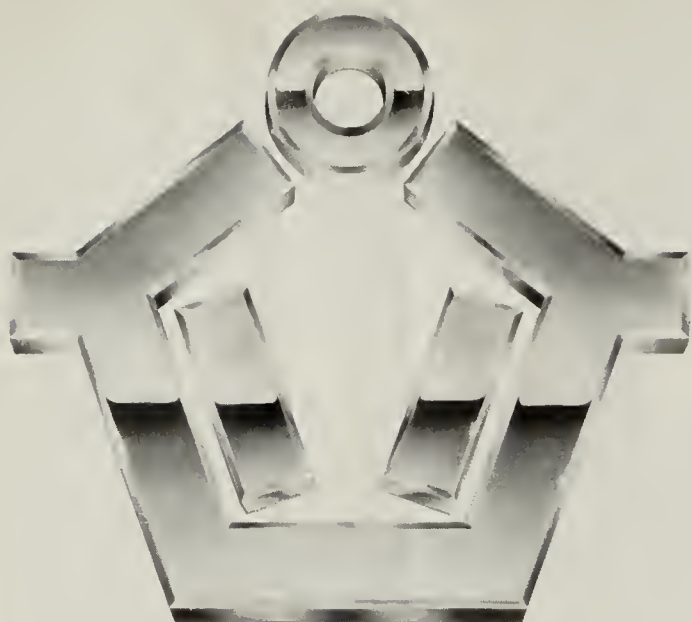
One Of A Kind



Zantac[®]
ranitidine HCl/Glaxo 150 mg and
300 mg tablets

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/ROCHE



One Of A Kind

Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.

2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H₂-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

BRIEF SUMMARY

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990



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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

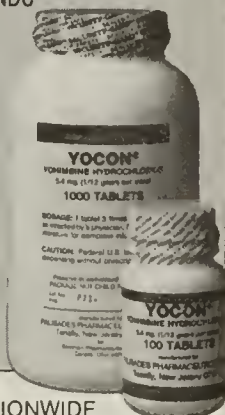
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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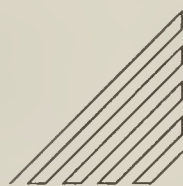
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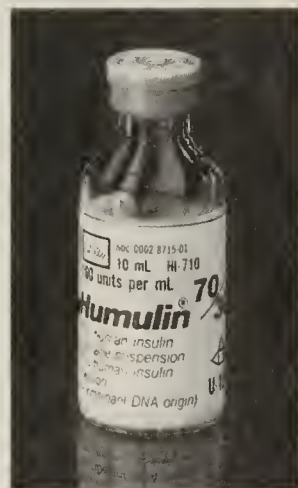
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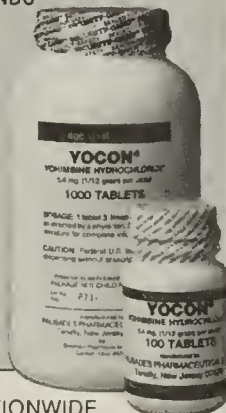
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1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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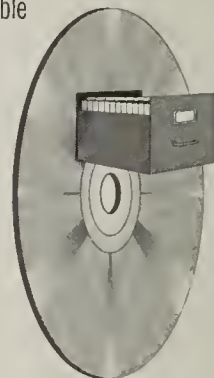
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COMMENTARIES

Tuberculosis in the AIDS era: A new threat from an old disease

Since 1981, when the first cases of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia were reported among homosexual men in New York City and California,¹ the acquired immunodeficiency syndrome (AIDS) epidemic has expanded in a manner that would have been difficult to imagine at that time. In addition to the increasing numbers of reported AIDS cases, the spectrum of clinical illness now recognized to be associated with human immunodeficiency virus (HIV) infection has broadened over the past decade as well. On a global basis, tuberculosis is clearly the most important serious and life threatening infection now known to be HIV-related which was not included in the original AIDS case definitions.²⁻⁴ It is believed that tuberculosis in the setting of HIV infection most commonly represents the reactivation of latent tuberculous infection secondary to HIV-induced immunosuppression.^{5,6} In populations in which high levels of HIV and *Mycobacterium tuberculosis* infection co-exist, one may predict that existing tuberculosis control efforts will be seriously threatened. Indeed, in sub-Saharan Africa and certain other regions of the developing world, alarming reports have suggested that millions of individuals may be co-infected with HIV and *M tuberculosis*, with the result that a resurgence in tuberculosis has become a major public health problem in these areas.^{2-4,7}

In the United States, tuberculosis incidence has been increasing since 1986, after decades of steady decline, a phenomenon which at least in part has been due to the current epidemic of HIV infection in this country.^{8,9} The recent increase in tuberculosis has occurred mostly among blacks and Hispanics in the 20-44-year-old age range, especially in populations and areas where HIV infection is also known to be concentrated.^{8,9} The Centers for Disease Control (CDC) recently released HIV seroprevalence data from a national sample of tuberculosis clinics, showing that from 13% to 46% of patients with tuberculosis were also infected with HIV in certain cities in the northeast and southeast.¹⁰ The highest levels were seen in New York City.¹⁰ These levels of co-infection are similar to what have been described in parts of central Africa.²⁻⁴ It is

estimated that there are at least ten million persons infected with *M tuberculosis* and one million persons infected with HIV in the United States; areas where these infections co-exist may be expected to be prime sites for a new increase in tuberculosis incidence.^{11,12}

New York City has been one of the areas most heavily affected by HIV infection and tuberculosis in the United States. The proportion of total United States tuberculosis cases accounted for by New York City rose from 4.6% to 9.8% between 1978 and 1987, during the same time period that HIV infection was spreading rapidly among drug users and their contacts in many of the same inner city communities.⁸ In 1989, tuberculosis incidence was 176 per 100,000 in central Harlem and exceeded 90 per 100,000 in parts of the south Bronx and Brooklyn; the United States case rate in 1987 was 9.3 per 100,000 (and was estimated for 1989 at 9.5 per 100,000).^{8,13} Total New York City tuberculosis incidence doubled between 1980 and 1989, with a 1989 rate of 36 per 100,000.¹³ Tuberculosis among children, long considered a sentinel marker for the spread of tuberculosis in a community,¹⁴ has also been increasing in New York City, further substantiating the current epidemic nature of tuberculosis there.¹⁵ Regarding the extent of HIV infection in New York City, among the most useful data are those from an ongoing statewide HIV seroprevalence survey initiated in 1987 by the New York State Department of Health, which involves anonymous, unlinked HIV antibody testing of all newborns.¹⁶ This methodology permits a direct estimate of HIV infection levels among childbearing women. Data from this study indicate that 1.25% of all childbearing women in the city are currently HIV-infected; levels of 2-3% or higher have been found in some areas of the city, predominantly in poor communities in Harlem, the Bronx, and Brooklyn with large black and Hispanic populations and a disproportionately high number of AIDS cases among intravenous drug users and heterosexuals,¹⁶⁻¹⁸ (R. Stricof, personal communication, February 1991).

The data cited above should bring a sobering perspective to any discussion of HIV infection, tuberculosis, and

their current implications for clinical medicine and public health. When one considers communities in New York City where tuberculosis has historically remained an endemic infection, even as it has markedly decreased in other areas, and one superimposes HIV infection on 2% or more of the young adult population, then the conditions for a dramatic upturn in tuberculosis cases are in place, with striking similarity to certain regions in the developing world. When one then adds the factors of poverty, homelessness, and lack of early access to medical care, the urgency of this health crisis becomes even more apparent. It must also be noted that the potential spread of HIV associated tuberculosis is ultimately wider than that of HIV itself, since horizontal transmission of tuberculosis may be expected to involve household members, health care workers, other institutional employees, and additional non-intimate contacts of index cases.

In this issue of the *Journal*, Lin and Goodhart¹⁹ describe characteristics of tuberculosis cases in a population of HIV infected patients at a large municipal hospital in East Harlem. Their report indicates the important role of tuberculosis in HIV associated morbidity in this population, in which 13% of 1,290 known HIV infected patients were diagnosed with active tuberculosis over a four-year study period. In addition, this paper corroborates known associations between certain demographic factors and tuberculosis in New York City, with an increased proportion of cases seen in this study among males, blacks, and those in the mid- to late-30s age range.

Surveillance data and clinical investigations suggest that among patients diagnosed with both tuberculosis and AIDS, these events tend to cluster together temporally, with tuberculosis generally, though not always, preceding actual AIDS-defining illnesses by a mean of several months.^{6,20-23} This is consistent with the fact that *M tuberculosis* is a more virulent organism than those causing the standard AIDS-defining opportunistic infections, including other, normally less pathogenic mycobacteria such as mycobacterium avium complex (MAC). The result is that *M tuberculosis* may cause clinical disease at earlier stages of immunosuppression. In the study of Lin and Goodhart,¹⁹ even though the authors were unable to determine the exact temporal relationship between patients' clinical status and the diagnoses of tuberculosis, a substantial proportion of their patients (especially blacks) were not yet in the later stages of symptomatic HIV infection by study end. In the CDC's 1987 revised AIDS surveillance case definition, extrapulmonary but not pulmonary tuberculosis is considered an AIDS-defining illness in HIV infected persons, reflecting the supposition that tuberculosis is more likely to indicate advanced immunosuppression when it is not confined to the lung.²⁴ This distinction was supported by a recent study which found that CD4 counts were lower in HIV infected patients with extrapulmonary tuberculosis than in those with pulmonary involvement only.²⁵ Current experience and guidelines would suggest, then, that pulmonary tuberculosis, while clearly HIV related, should not necessarily be considered AIDS equivalent in HIV infected patients, in terms of its prognosis or implications for survival.

Tuberculosis in the setting of HIV infection indeed generally responds well to standard chemotherapy, although

there has been debate over the necessary duration of treatment.^{5,23,26-28} There is also clear consensus that isoniazid chemoprophylaxis for latent tuberculous infection should be pursued aggressively in HIV infected patients, in light of the increased risk of reactivation, although here as well the question of treatment duration is unresolved.^{5,6,28} Current CDC guidelines suggest that HIV infected individuals receive regular tuberculin skin testing; isoniazid prophylaxis for at least 12 months is recommended for all eligible patients with ≥ 5 mm of induration on intradermal (Mantoux) tests (less than the normal standard of ≥ 10 mm induration), and with no distinction made for persons over 35 years of age.⁵ One recent study from Zambia, a prospective randomized trial of isoniazid versus placebo involving over 500 HIV infected patients, found that tuberculosis incidence was significantly decreased in the treated group, in a population with high levels of latent tuberculous infection; 8.3% of the placebo group and none of the treated patients developed active tuberculosis over one year.²⁹ Another study from New York City, while not designed as a randomized trial, found that active tuberculosis did not develop in HIV-infected intravenous drug users with prior positive tuberculin tests (PPD) who had received isoniazid prophylaxis, compared with those who had not been treated.⁶ Among HIV infected patients with positive PPD tests in this study, the overall rate of active tuberculosis was 7.9 cases per 100 person-years. These findings underscore the critical importance of routine tuberculosis screening, case identification, and preventive therapy in HIV-infected populations in areas where tuberculosis is also endemic.

Tuberculosis control efforts in the AIDS era must also address pressing issues concerning diagnostic technology and environmental sanitation. The possibility of rapid diagnostic tests for *M tuberculosis*, (eg, species-specific DNA probes, monoclonal antibodies, serologic tests, and polymerase chain reaction [PCR] techniques), has not yet been realized in clinical practice. However, such tests may soon afford a great advantage in efforts to institute early therapy, with major implications for clinical outcome and disease control.³⁰⁻³² Particularly in HIV infected patients, in whom mycobacteria other than *M tuberculosis* are commonly found, the ability to rely on specific, immediate diagnostic techniques beyond simple acid-fast smears would be a powerful clinical intervention. Environmental interventions, involving adequate ventilation, facilities for respiratory isolation, and consideration of ultraviolet light air disinfection in hospitals and other high-risk institutional settings, must also become key elements of tuberculosis control efforts and planning.^{30,33,34} Some of these measures hark back to an earlier era when tuberculosis was more widely recognized as a major public health problem. They have become equally relevant at the present time. Indeed, with recent reports of nosocomial transmission of *M tuberculosis* (including multiple-drug resistant strains) to patients and staff in AIDS treatment facilities, one is reminded that the limited routes of parenteral transmission of HIV afford no protection against the respiratory spread of HIV associated tuberculosis to non-intimate contacts.³⁵⁻³⁷

An effective public health response to these dual epidemics must address two divergent types of diseases and associated transmission dynamics: a blood-borne and sex-

ually transmitted disease, involving activities which remain highly stigmatized and for which reduction in transmission requires promotion of personal behavior change; and a respiratory pathogen whose control may depend more heavily on environmental measures and aggressive identification, chemoprophylaxis, and treatment of infected individuals. While case-finding and partner notification strategies central to past approaches to controlling sexually transmitted disease have been adopted increasingly with respect to AIDS, one must be sensitive to the important issues of confidentiality, denial, fear, and stigma which surround HIV infection at the present time. These may become increasingly relevant factors as control efforts are intensified to prevent the spread of HIV associated tuberculosis. One must hope that the paradigmatic approaches to these two epidemics will be complementary and not competing, so that the strategies required to control either one will not compromise efforts to address the other.

The Advisory Committee for the Elimination of Tuberculosis (ACET) has set the goal for the United States to reduce the incidence of tuberculosis to 3.5 cases per 100,000 by the year 2000, and to eliminate tuberculosis by the year 2010.³⁰ In communities such as the one described by Lin and Goodhart¹⁹ in this issue of the *Journal*, where rates of tuberculosis and HIV infection are among the highest in the country, this goal may seem at present to be an illusory one. Historical data on tuberculosis incidence in the United States show that the black-white disparity in tuberculosis incidence was steadily increasing for several decades even prior to the AIDS epidemic.⁸ These data, along with compelling recent information on mortality in general in the Harlem illnesses,³⁸ suggest that tuberculosis and other conditions affecting such areas are not equal opportunity diseases, but are in fact inseparable from poverty, racial inequity, and other social and economic conditions which pose a fundamental threat to public health. While the issue of differential racial susceptibility to tuberculosis has recently been raised, debated, and alluded to by the authors of the current report,^{19,39,40} such arguments may come close to ignoring the underlying societal factors which clearly have their own profound impact on the transmission and expression of both HIV and *M tuberculosis*. Until these nonbiologic factors are addressed, efforts to control either one of these epidemics will remain short-sighted at best, and ineffective and counterproductive at worst. Unless the effort to promote public health is only one component of a broader societal agenda to promote public good, the goal of eliminating tuberculosis as well as AIDS will remain elusive.

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The physician and the poor

Dr Thomas Weil is to be commended for his incisive article in the current issue of the *Journal*.¹ In my view he has helped to clarify the narrowing choices available to the American people as they confront the dual challenge of providing coverage for the 37 million persons who are currently uninsured and of moderating, if not reducing, the nation's steadily increasing expenditures for health care. He has called attention to many critical issues that are central to the policy choices ahead and has suggested the likely impact of many of these choices on the future practice modes and earnings of physicians. Although I do not agree in all respects with Dr Weil's analysis, I can report that it ranks among the best recent contributions to this burgeoning literature.

Dr Weil, like most health policy analysts, develops his analysis almost exclusively from the demand side of the equation—that is, in terms of shortcomings in health care coverage, the flow of funds from different payor sources, cross-subsidization, and the potential of many hospitals to meet future payments on their outstanding bonds. I want to call attention to the much neglected supply side of the policy dilemmas that we face in seeking to provide universal coverage and at the same time effectively control our health care expenditures.

In the last 30 years, we have increased the physician supply from about 140 per 100,000 population to over 240 per 100,000, a ratio that will rise to 265–270 per 100,000 by the end of the decade. In short, the growth in the physician supply, now 70%, will reach 85% in the year 2000. One of the principal reasons for this spectacular increase was the widespread consensus that the nation needed more physicians so as to ensure that all persons could obtain needed medical care, a position that the American Medical Association (AMA) also espoused after 1968.² The proponents of an expanded physician supply never stopped to consider that, short of compulsion or very powerful incentives such as the liberal cancellation of educational indebtedness as a *quid pro quo* for service in a shortage area, physicians would shun practicing in a neighborhood or a community where they did not see much prospect of earning a livelihood. The resistance of a spouse or concerns about the educational opportunities for one's children reinforced these considerations of income.

The question of how low income and minority groups can obtain access to physicians is of critical importance to the nation but the belief that the solution is to be found in the rapid expansion of the physician supply is demonstrably naive. From my perspective, the aim should not be to pressure physicians to practice where they cannot make a reasonable living. Rather, it would be preferable to adopt a systems approach designed to facilitate access of the poor to institutional settings where physicians are willing to practice, such as community health clinics and hospi-

tals, and making sure that means of transportation, hours of operation, and other factors that may alternatively encourage or inhibit access are optimized. In many instances nurse practitioners can serve as important initial contacts between the patient and the health care system.

Although the very large increase in the number of physicians during the past three decades did not significantly alleviate the barriers to access for many of the poor and the underserved, what did it accomplish? I would first point to the wide diffusion of specialists and subspecialists from the large metropolitan centers to the suburbs and more generally to medium-size and even smaller communities, with 25,000 to 50,000 inhabitants.³ There are few nonmetropolitan communities that have not enjoyed an order-of-magnitude improvement in the quality of medical care, both ambulatory and in-patient, available to their local populations.

The diffusion of well-trained physicians to the outlying areas was the fulcrum for the parallel upgrading in the local hospitals which are now capable of providing a high level of in-patient care for all except the most esoteric conditions. It is a matter of no small concern, however, at least to the economist, that the much expanded and better staffed hospital plant operates currently at an average occupancy of 65% or so, and the shift from inpatient to ambulatory care has surely not run its course.

Health services researchers have estimated that physicians (and dentists) are responsible by the decisions they make for about 75% of all health care costs that are incurred in the course of a year. Accordingly, it is of real consequence whether there are too many physicians in active practice. Had we increased the physician supply between 1960 and 1990 by 30% instead of 70%, the health care expenditures of the United States in 1990 might have been lower by 30% (75% of the incremental 40%). On a denominator of \$675 billion, the US Department of Commerce estimate of total expenditures for the year 1990, this translates into a differential of about \$200 billion. The fact that we "overproduced" physicians to such an extent represents a structural challenge of major proportions in seeking to moderate health care expenditures. The second closely related challenge is to shrink the excess hospital plant that exists in most locations. Of course, New York City, with its spectrum of new morbidities, from acquired immunodeficiency syndrome (AIDS) to crack-addicted and abandoned "boarder" babies, is an exception.

A related issue: In 1940 the total national outlay for biomedical research came to \$45 million, of which the US government contributed \$3 million. In 1990, the comparable outlays were \$20 billion with the federal government covering half. Even if one makes a liberal adjustment for the depreciation of the dollar (ten-fold), the increase is

impressive—from \$450 million to \$20 billion, or more than 44-fold.⁴ Clearly, such a large investment in biomedical research and development (R&D) has as its aim improved therapeutics. However, with occasional exceptions (the development of polio vaccine, for example), the improvements are cost accelerating, not cost saving.

In sum, from the vantage of the supply-side economist, any serious commitment to contain medical care costs would necessitate serious efforts to control the physician supply, reduce the hospital plant, and slow the pace of the nation's efforts to cure the dread diseases such as heart disease, cancer, and stroke.

What can we *reasonably* expect? In my opinion, physicians' earnings are likely to decline in the decades ahead; nevertheless, we will not be in a position to reduce the supply. I anticipate a considerable shrinkage in the hospital plant and more regulation to limit the diffusion of costly services. However, I suspect that the American people will act as a spur to higher health care expenditures concomitant with improved therapeutics and outcomes.

We should be able without too much trouble to develop a system of universal coverage: that is the easy part of the challenge confronting us. The other half of the challenge is much tougher: How do we rein in the increases in annual expenditures so that they do not continue to outstrip the growth in gross national product (GNP) by a large margin? President Richard Nixon warned we were in a crisis in 1969 when national health expenditures totaled \$75 billion, 7.5% of GNP. According to the federal government's forecast we are on our way to an outlay of \$1 trillion in

1995 which may amount to 15% of our GNP, and conceivably more thereafter. Clearly, we are entering the arena where difficult decisions can no longer be avoided. Each of the principal parties—government, physicians, and the public—will have to become reconciled to the fact that the halcyon post-Medicare-Medicaid years are ended and that all of us must deal with a new and less pleasant reality. The real discipline that we face is to ensure that in seeking to control costs we do not seriously undermine a medical care system that has contributed much to the well-being of the American people and has the capacity to contribute a great deal more in the future.

The physician community must realize that if it seeks to hold on to all that it now has, not only will it fail but it will jeopardize the future of American medicine which, under effective leadership, can continue to better the health and lives of all Americans.

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Atypical infections of the hand and wrist

Atypical infections of the hand and wrist pose a serious diagnostic challenge to physicians.^{1,2} These infections are rare and preclude any physician from becoming expert in their diagnosis and management. It has been by means of a number of small series and isolated case reports that a rather substantial volume of information regarding the diagnosis and treatment of these rare conditions has been developed.³⁻¹⁴

Though atypical hand and wrist infections are rare, the literature documents the severe consequences of delay in diagnosis or inadequate treatment of these infections. The morbidity and decreased function as a result of delay in diagnosis and treatment has a major impact on the life of the patient. Long neglected or undertreated cases frequently result in destroyed hand function or amputation of parts. This is often the case with mycobacterial and atypical mycobacterial infections of the hand. When dealing with rare necrotizing infections, such as necrotizing fasciitis, even the life of the patient may be in jeopardy if the diagnosis is delayed. Assembling a body of information regarding the diagnosis and rational treatment of these rare conditions is, therefore, a worthwhile endeavor. Reports such as that by Gluck et al¹⁵ in this issue of the *Journal* supplement our knowledge on the subject. Thus,

they represent a valuable contribution to the literature for the practicing physician.

The literature to date on atypical infections of the hand and wrist offers the physician a rational approach to diagnosis and management. Atypical hand infections can be broadly classified into two categories; acute necrotizing infections that are generally produced by synergistic bacteria or virulent strains of streptococci in conjunction with a compromised host, or indolent, slowly progressing infectious processes produced by mycobacteria or fungi. Necrotizing infections are easy to recognize, but demand prompt diagnosis and aggressive treatment. A more disturbing problem is the indolent mycobacterial and fungal infections which often slowly progress for years, resulting in permanent loss of hand function.^{4,5,8}

The following principles are suggested for the management of these indolent atypical hand infections. These principles involve early diagnosis and adequate treatment. Early diagnosis requires a high index of suspicion and properly obtained tissue for culture, stain, and sensitivity by the surgeon. Frequently, obtaining the proper tissue means entering a tendon sheath or joint to obtain an adequate specimen of synovial tissue. Once the proper diagnosis has been made, the literature clearly indicates that a

combined approach of adequate surgical debridement and long term antimicrobial or anti-fungal treatment is most successful. Medical treatment alone in the absence of adequate surgical debridement is frequently inadequate. Conversely, aggressive surgical treatment not accompanied by adequate antimicrobial treatment of sufficient duration is also likely to fail.

Today we are capable of performing reasonably radical surgical debridement of tendon sheaths and joints without producing long term damage to the hand. This is possible because of a higher level of skill on the part of surgeons trained in the care of the hand, and advances in postoperative hand therapy. We are also fortunate to have available a large number of well-trained infectious disease specialists with current knowledge of the best treatment regimes for these atypical infections. Adequate treatment of these conditions requires a multidisciplinary approach consisting of a surgeon skilled in the treatment of hand conditions and an infectious disease specialist knowledgeable about atypical infections.

My recommendation to the practicing physician in 1991 would be to obtain access to the tremendous information now present in the literature on these rare conditions. One should apply the principles that have been laid out over the years by virtue of many small series and case reports and have a high index of suspicion. Adequate tissue should be obtained and properly handled to facilitate definitive diagnosis. Once the diagnosis is made, aggressive and complete surgical debridement of the infected portion of the hand should be instituted. Infectious disease consultation should be utilized for optimal antimicrobial or antifungal treatment, and that treatment should be continued for a sufficient period of time. Overtreatment of these highly resistive and morbid conditions is preferable to undertreatment.

Successful treatment guidelines for most strains of atypical mycobacteria and fungi can be found in the literature. The large numbers of patients with the acquired immunodeficiency syndrome and the greater use of im-

munosuppressive therapy will undoubtedly increase the importance of these atypical infections.¹⁶ They will remain rare in the hand and wrist, and require a high index of suspicion on the part of physicians if they are to be diagnosed.

Dr Gluck and his colleagues have made an important contribution to the literature on tuberculosis of the hand and wrist. We should all avail ourselves of this expanding literature so as to more successfully diagnose and treat these rare but important conditions.

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Population characteristics of tuberculosis in an HIV/AIDS registry from an East Harlem Hospital

ROBERT Y. LIN, MD, PAUL T. GOODHART, MPH

ABSTRACT. The recent increase of tuberculosis nationally and in New York City has been attributed in part to the progression of the acquired immunodeficiency syndrome (AIDS)/human immunodeficiency syndrome (HIV) epidemic. The East Harlem/South Bronx/Bushwick sections of New York City have an especially high incidence of tuberculosis. An HIV/AIDS registry (1986–1990) consisting of 1,312 patients from a community hospital serving East Harlem was examined for population characteristics associated with documented tuberculosis in the registrants. Tuberculosis affected males more commonly than females and was observed in comparable frequency in patients with AIDS-related complex (ARC) (12.9%) and AIDS (15.0%). The proportion of cases in blacks (18.3%) was significantly greater than that in Hispanics (10.4%, $\chi^2 = 15.196$, $p = 0.0003$) or whites (8.7%, $\chi^2 = 5.62$, $p = 0.0171$). Among intravenous (IV) drug users, the proportion of tuberculosis cases was also significantly higher in blacks than in Hispanics. These data could be consistent with a difference in exposure to tuberculosis and/or the purported racial susceptibility of blacks to tuberculosis infection. A review of new tuberculosis cases in East Harlem also suggests that blacks are at a greater risk for developing tuberculosis than Hispanics.

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Recent studies by the New York City Department of Health have identified a high rate of reported tuberculosis cases in an acquired immunodeficiency syndrome (AIDS) registry for the years 1981 through 1985.¹ They have also demonstrated an increasing incidence of tuberculosis in the total New York City population since 1985 compared to 1981.² Many of these cases have occurred in the disadvantaged areas of the city which are known to have a high number of individuals who use intravenous (IV) drugs, are non-white, and are homeless. A high incidence of tuberculosis is reported to be associated with these characteristics.^{1,3–5} These areas of New York City are also known to have a high incidence of human immunodeficiency virus (HIV) infection and AIDS.⁶ This has led to the suggestion that HIV infection complicated by tuberculosis may actually be influencing the city's rising incidence rates of tuberculosis.^{7,8}

In view of the increase in tuberculosis, especially among disadvantaged populations of New York City, we reviewed the AIDS registry of a community hospital serving East Harlem (also known as "Spanish Harlem") in order to characterize tuberculosis complicating primarily symptomatic HIV infection.

METHODS

The HIV/AIDS registry consisted of a data base compiled by the Metropolitan Hospital AIDS Program. Data on primarily hospitalized patients with AIDS and AIDS-related complex (ARC) were acquired by members of this program through active surveillance of daily admission cases by diagnoses, and weekly discussions of new and old AIDS/ARC cases by a multidisciplinary AIDS team. Cases related to HIV infection were identified and confirmed by clinical data in the charts. Cases with AIDS defining diagnoses (see below) and/or with a positive HIV antibody test were added to the HIV/AIDS data base. Patients with a risk factor and clinical symptoms suggestive of HIV infection were also followed but were not logged as registry patients. Follow-up for all patients consisted of weekly chart review on initial and subsequent admissions. This HIV/AIDS data base was started on January 6, 1986. The cumulative cases through March 8, 1990, were considered, and included 34 cases before 1986. The total number of cases studied was 1,312. AIDS cases were diagnosed using Centers for Disease Control (CDC) surveillance criteria.^{9,10} The 1987 revisions of the CDC criteria for AIDS¹⁰ were not applied to cases completely logged before revision announcements. The 1986 CDC classification¹¹ was used to stage HIV disease according to the final group for each patient, except that patients with oral candidiasis without other AIDS defining criteria were classified as group III and not as group IV. These modified groups of II, III, and IV are henceforth referred to as asymptomatic, AIDS-related complex (ARC), and AIDS in this text. Seven patients could not be classified due to a lack of essential data, thus leaving 1,305 patients for analyses and subsequent description. Although the registry was not designed to identify or screen asymptomatic HIV infected patients, 84 asymptomatic cases (mostly spouses of index cases) were diagnosed by the multidisciplinary AIDS team physicians and were also included in the data base.

Tuberculosis cases among registry patients were defined as being active by bacteriologic culture results from Metropolitan Hospital, or by communication with another hospital or public health clinic that had recently instituted anti-tuberculous therapy (≤ 9 months) and had obtained bacteriologic evidence of tuberculosis. A total of 174 cases of active tuberculosis were thus identified. While cases with a remote history of tuberculosis were not considered in the analysis relating to tuberculosis, histories of prior tuberculosis could not be excluded in a few patients due to psychiatric or neurologic impairment and/or lack of available past medical records, but were included as active tuberculosis cases. Seven other cases clinically diagnosed as tuberculosis without obtainable bacteriologic confirmation were excluded

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from the analyses relating to tuberculosis only. (Department of Health registries for active or incident tuberculosis could not be obtained and thus were not used for comparison with the documentation of tuberculosis described here).

The patient characteristics recorded in the HIV/AIDS data base included the following: date of birth, date of entry into the data base (most often the date of first admission), sex, ethnicity, mode of transmission, zip code (if domiciled), dates of admission, opportunistic infection, HIV related neoplasia, sexual history/preference, a continuously updated staging classification, and presence of tuberculosis. The presence of tuberculosis was recorded in the HIV/AIDS data base since its initiation. HIV staging classification and date at the time of diagnosis of tuberculosis were not recorded due to the method of continuous updating of data into the data base. The analysis of differences between different subpopulations was made using contingency tables (2x2) and chi squared (χ^2) analyses on the PC Statistician™ program (Human Systems Dynamics, Northridge, Calif). The Mantel-Haenszel chi-square (χ^2_{MH}) test was used to analyze the effect of intravenous drug abuse on the distribution of tuberculosis, correcting for major groupings of ethnicity.¹³ Confidence intervals for odds ratios were calculated using the test based method.¹² Confidence intervals for relative risks were calculated using the method of Katz.¹³

RESULTS

The geographic distribution of all HIV/AIDS registry patients was similar to that of tuberculosis patients. The majority of all cases with permanent addresses resided north of 96th Street. Fifty percent of cases were living in the two zip code areas (10029 and 10035) which corresponded to East Harlem (bordered by Fifth Avenue, the East River, East 129th Street, and East 97th Street). Most tuberculosis cases with identifiable zip codes resided north of 96th Street, and 47% of cases for whom zip codes were available resided in the two East Harlem zip code areas. Fifty-six percent of all patients did not have a permanent residence, compared to 55% of tuberculosis patients. The ethnic/racial make-up of the total HIV/AIDS registry included 103 (7.9%) whites, 486 (37.2%) blacks, and 701 (53.7%) Hispanics. There were more Hispanics than blacks for the subpopulation of patients without permanent residences (420 Hispanics to 241 blacks), as well as for those with permanent residences (263 to 185). The increase of HIV/AIDS registry patients for calendar years 1986-1989 was accompanied by an increase in tuberculosis seen in each year's registrants (Fig 1).

Of all classified HIV/AIDS registry patients, 649 (49.6%) were staged as ARC and 572 (43.8%) as AIDS. Eighty-four ARC patients had tuberculosis compared to 86 AIDS patients. Stratifying the asymptomatic, ARC, and AIDS patients by major ethnic group (Table I) revealed a greater proportion of ARC to AIDS-associated tuberculosis cases in blacks compared to whites or Hispanics ($\chi^2 = 11.16, p = 0.0013$). The presence of any of three major opportunistic infections (*Mycobacterium avium-intracellulare*, *Pneumocystis carinii*, and *Toxoplasma gondii*) were not associated with the presence of tuberculosis. The majority of patients (85.1%) with tuberculosis were between the ages of 25 and 48 years, with a mean age of 37 years. This distribution showed a somewhat greater proportion of

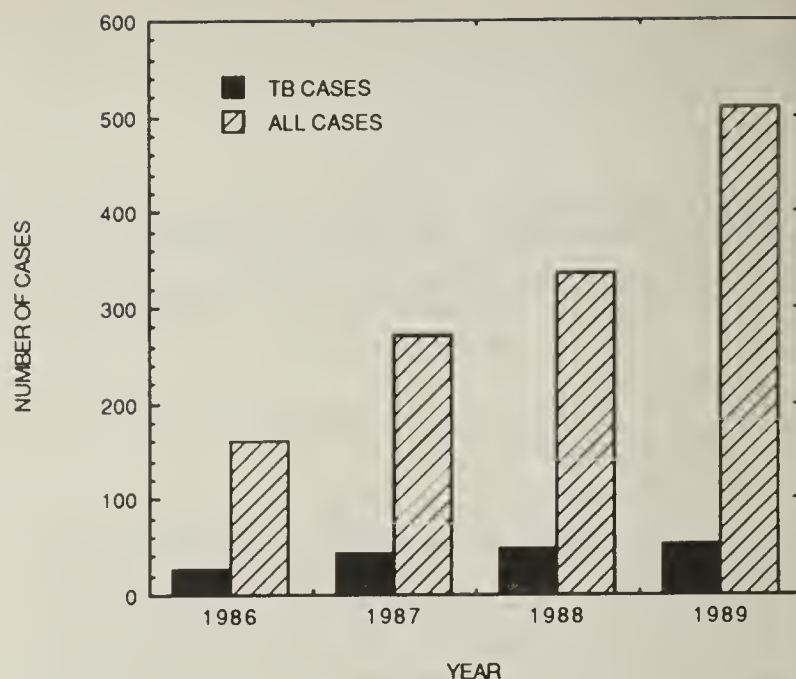


FIGURE 1. Number of HIV/AIDS registry patients, and registry patients with tuberculosis, 1986-1989.

older patients than that seen with the entire HIV/AIDS registry (Fig 2), which had a mean age of 34. The mean age for all blacks and all Hispanics was similar (35 and 34 years of age, respectively). IV drug use was reported in 940 (72.0%) of all HIV/AIDS registry cases, and in 340 blacks and 534 Hispanics. There was no statistical association between IV drug use and the presence of tuberculosis ($\chi^2_{MH} = 3.28, p > 0.05$) (Table II). Males showed a higher proportion of tuberculosis than females (15.1% versus 7.7%, $\chi^2 = 11.438, p = 0.0011$).

The proportion of tuberculosis cases in blacks (Table II) was significantly higher than that observed with Hispanics ($\chi^2 = 15.196, p = 0.0003$) or whites ($\chi^2 = 5.62, p = 0.0171$). When only the cases associated with IV drug use (Table II) were considered, the difference between blacks and Hispanics remained ($\chi^2 = 18.076, p = 0.0001$). The odds ratio for tuberculosis in blacks compared to Hispanics was 1.93 (95% confidence interval 1.39, 2.68), while that for blacks compared to whites was 2.34 (95% confidence interval 1.16, 4.73). Whites did not significantly differ from Hispanics. Three tuberculosis cases occurred in patients (N = 15) not belonging to these three racial/ethnic groups.

DISCUSSION

Infection with tuberculosis involves a host defense response consisting of cell mediated immunity. It is thus logical that conditions associated with diminished cellular immunity are also associated with an increased incidence of tuberculosis. The association of tuberculosis with AIDS is now well recognized and may be as high as 4-10% of

TABLE I. Stratification of Racial/Ethnic Categories With and Without Tuberculosis (TB) by Staging Group*

Racial/Ethnic Category	Asymptomatic	ARC	AIDS	Total
Blacks with TB	3 (3.4%)	54 (60.7%)	32 (36.0%)	89
Blacks without TB	26 (6.5%)	190 (47.9%)	181 (45.6%)	397
Hispanics with TB	1 (1.4%)	26 (35.6%)	46 (63.0%)	73
Hispanics without TB	48 (7.6%)	323 (51.4%)	257 (40.9%)	628
Whites with TB	0 (0%)	3 (33.3%)	6 (66.7%)	9
Whites without TB	6 (6.4%)	50 (53.2%)	38 (40.4%)	94
Others with TB	0 (0%)	1 (33.3%)	2 (66.7%)	3
Others without TB	0 (0%)	2 (16.7%)	10 (83.3%)	19
Total	84 (6.4%)	649 (49.7%)	572 (43.8%)	1,305

* Row percentages shown in parentheses.

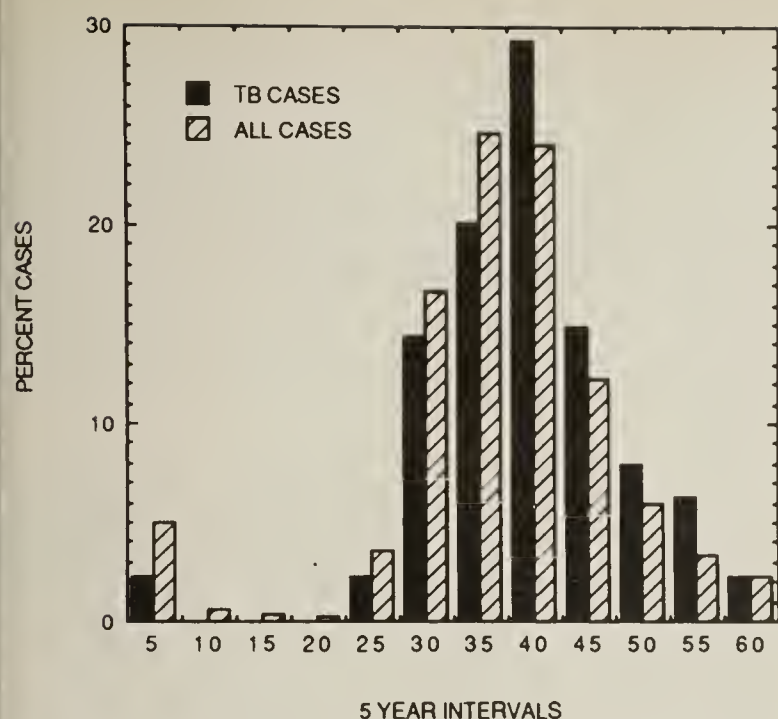


FIGURE 2. Age distributions for all HIV/AIDS registry patients and those with tuberculosis. Fourteen (1.07%) of the total cases (hatched bars) were older than age 59 and are not represented in this chart.

reported AIDS cases depending on locality.⁸ The magnitude of tuberculosis cases occurring in the setting of HIV infection is thought to influence total incidence rates in certain parts of the United States,⁸ especially in the northeast. The importance of this assertion is underscored by the fact that the national trend of declining tuberculosis incidence showed a change in its downward slope in 1985,¹⁴ a year in which New York City also started to see an increase in the incidence of tuberculosis. Associations with the development of tuberculosis have also included the use of IV drugs, being black or Hispanic, and being homeless.³⁻⁵ A higher risk for developing tuberculosis for blacks and Hispanics has also been observed in children,² for whom the incidence of tuberculosis rose progressively in 1987 and 1988. Since New York City has a large proportion of children belonging to these ethnic groups, a new policy was recently instituted to screen all elementary school children with the Mantoux test in order to identify all those with asymptomatic and/or unreported and untreated clinical infection with *M tuberculosis*.

The prevalence of tuberculosis in HIV infection and the natural history of latent tuberculosis in HIV infection is not well defined. One two-year study of tuberculin skin test positive methadone clinic patients showed a significantly higher rate of tuberculosis in those who were HIV antibody seropositive compared to those who were HIV antibody seronegative.¹⁵ This suggests that tuberculin

skin testing can be used to identify HIV antibody seropositive individuals who are at a higher risk for developing tuberculosis. The CDC has thus recommended screening HIV infected individuals for tuberculosis in hopes that prompt prophylactic treatment can prevent the development of many cases of tuberculosis and that active cases can be treated earlier.⁸

National tuberculosis data from 1988¹⁴ show that Hispanics had an incidence rate four times that of whites, while blacks had a 6.9 times greater incidence rate than whites. In the HIV/AIDS registry we studied, the proportion of tuberculosis cases in Hispanics was similar to that seen in whites, while blacks had an increased proportion of tuberculosis compared with both whites and Hispanics. Thus it is not clear from these data that Hispanics with HIV infection are at greater risk than whites for developing tuberculosis. These ethnic differences raise the possibility that blacks may have a higher incidence of latent infection due to higher exposure, which in the presence of HIV infection leads to a higher incidence of clinical tuberculosis. However, it has been shown that blacks have a significantly higher risk for developing latent tuberculous infection compared to whites under similar exposure circumstances.¹⁶ Thus it is also conceivable that blacks have a higher susceptibility to latent tuberculous infection in the setting of exposure equivalent to that of non-blacks, which subsequently leads to a higher incidence of active tuberculosis. Although it has been suggested that tuberculosis occurring in the setting of HIV infection probably represents reactivation of a latent tuberculous infection,⁸ the relative importance of exposure and susceptibility remains to be defined in these disadvantaged populations. A more advanced stage of HIV infection in blacks could also predispose to a higher incidence of tuberculosis. The greater ratio of ARC to AIDS-associated tuberculosis cases observed among blacks compared to Hispanics (both with and without tuberculosis) suggests that there may be a greater disposition for blacks to develop active tuberculosis at an earlier stage of HIV infection compared to Hispanics.

It is of interest that in the New York City Department of Health AIDS/TB study¹ the odds ratio of tuberculosis in AIDS (1981-1985) for blacks compared to Hispanics was only 1.2 ($\chi^2 = 1.199$), while in this study it was 1.9. The AIDS/TB study and our described HIV/AIDS registry, however, have several differences including geographic specificity between a city-wide AIDS registry and a community hospital AIDS registry (which includes ARC patients); the racial composition of Hispanics with tuberculosis in East Harlem, which is overwhelmingly non-black; and the different years of study. Incident cases of

TABLE II. Presence of Tuberculosis (TB) in Major Racial/Ethnic Subpopulations*

	Race/Ethnicity		
	White	Black	Hispanic
All patients—TB present	9 (8.8%)	89 (18.3%)	73 (10.4%)
All patients—TB absent	94 (91.3%)	397 (81.7%)	628 (89.6%)
Only IV drug users—TB present	7 (11.3%)	71 (20.9%)	56 (10.5%)
Only IV drug users—TB absent	55 (88.7%)	269 (79.1%)	478 (89.5%)

* Noted with absolute numbers and column percentages.

tuberculosis by race/ethnicity in East Harlem from the years 1986 through 1989 (personal communication, Toni Davis, Bureau of Tuberculosis Control, New York City Department of Health, June 1990) were divided by the respective ethnic populations in this area (55,063 Hispanics and 36,736 blacks) from the 1980 census (personal communication, Chi Wa, Division of Vital Statistics, New York City Department of Health, July 1990) and revealed a consistent increased relative risk for developing tuberculosis in blacks compared to Hispanics (Fig 3). The actual number of incident cases for the years 1986, 1987, 1988, and 1989 were 33, 23, 36, and 32 for Hispanics; and 34, 27, 45, and 44 for blacks, respectively. The number of new non-Hispanic white cases observed in this area was ten or fewer each year. These calculations are based on an assumption that significant migration patterns in these ethnic subgroups did not occur, although travel to and from Puerto Rico is commonly observed in this population. This is again consistent with an increased risk for blacks developing tuberculosis in this area. It is not known what number of these patients had co-existing HIV infection. The similarity between the relative risk (calculated from Table I) for blacks compared to Hispanics observed in the HIV/AIDS registry (1.76) (1.32, 2.34; 95% confidence interval) and that observed with East Harlem (mean for the years 1986–1989 = 1.81) (1.43, 2.30; 95% confidence interval) suggests that the pattern of tuberculosis from Metropolitan Hospital may be representative of the community at large.

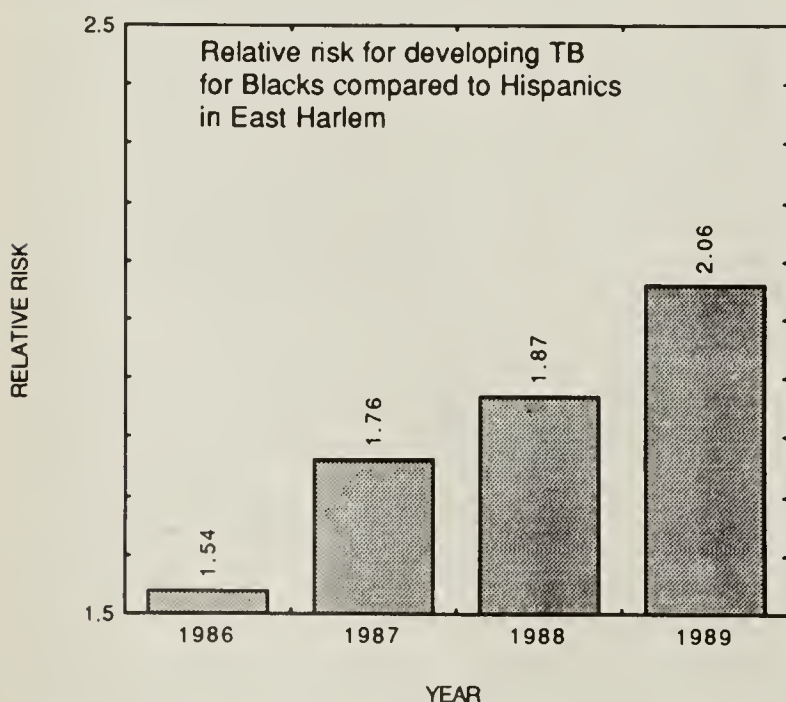


FIGURE 3. Estimated relative risk of developing tuberculosis in East Harlem for blacks compared to Hispanics.

The population studied here included a significant number of homeless patients. Other studies⁴ have reported prevalence rates of asymptomatic tuberculosis among the homeless to be as high as 22–50%, with clinical tuberculosis prevalence rates on the order of 1.6–6.8%. Both exposure and latent infection rates might therefore be expected to be high for this population. Since several reports have focused on the increasing rate of tuberculosis in Hispanic populations, it may be important to address inherent ethnic differences in host defenses against *M tuberculosis* for Hispanics in future studies, as has been examined in blacks.¹⁶

In view of the high risk for tuberculosis of certain disadvantaged populations in New York City, a more widespread screening approach may be needed for adults as well as children in these areas to reduce the prevalence of tuberculosis. A prospective study incorporating serial screening may also help to examine whether or not Hispanics have a different susceptibility to tuberculosis compared to other major ethnic/racial groups. Future studies examining the prevalence of HIV infection in tuberculosis cases will help define the contribution of HIV infection to the rising rate of tuberculosis both locally and nationally.

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First year medical student experiences with being discouraged from entering medical school

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ABSTRACT. Three hundred and fourteen first year medical students from two consecutive classes were surveyed for their experiences with being discouraged from entering medical school. Sixty-eight percent (215) had been discouraged from becoming physicians. The sources of discouragement were varied, with 43% citing physician acquaintances and 40% friends and neighbors. Parents were the principal source of encouragement (58%) followed by friends and neighbors (47%). More students (34%) were encouraged by undergraduate professors and advisors than by their family doctor (23%), a physician relative (18%), or a physician acquaintance (31%). Discouragement centered on three broad areas: diminished financial rewards, increased financial costs, and quality of life.

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The diminishing appeal of medicine as a professional career for young people has been a continuing source of concern.¹ The causes of this are several and include significant changes in the social environment and the practice of medicine, the cost and length of medical training, and medicine's less competitive appeal with other careers. The core of traditional values that makes the medical profession attractive includes a desire to be of service, significant independence in one's work, professional and social status above that of many other professions, an intellectual interest in science, and a secure and respectable income.² As the certainty of some of these values has declined, so, too, has interest in medicine as a career.

The dissatisfaction levels experienced by practicing physicians themselves are a matter of public knowledge. A 1989 survey conducted by the Gallup Organization for the American Medical Association found that only 24% of 1,004 physicians surveyed would definitely go to medical school. Another 36% said they would probably go. Some 14% said they would definitely not go and 25% said they would probably not go. Thus a significant 40% of the physicians sampled expressed the view that they would not choose or probably would not choose medicine as a career.³

The present survey was undertaken to determine when entering medical school freshmen had first decided on medicine as a career, whether they had been encouraged

to or discouraged from doing so, and the sources of encouragement and discouragement.

METHODS

Questionnaires using a fixed alternate and free response format were distributed during two consecutive years to the members of two first year classes. Participation was voluntary and anonymity assured. Of the 420 students in the survey group, 314 (75%) completed and returned the surveys, and these constitute the basis of the analysis presented here. Of the students surveyed, 189 (60%) were men and 101 (32%) were women. Twenty-four (8%) did not list their sex. Eighty-five (27%) said they were members of a minority group.

RESULTS

Seventy-four (24%) students had decided to study medicine in elementary school, 120 (38%) in high school, and 72 (23%) in college. The remainder made their decision after college, did not recall, or else did not give a response. Two hundred and three (65%) had been encouraged to study medicine compared to 99 (32%) who stated that they received no encouragement at all. Two hundred and fifteen (69%) had been discouraged from studying medicine while 90 (29%) had never received any discouragement at all.

The sources of both encouragement and discouragement were several (Table I). Parents prominently figured as sources of encouragement (58%), followed by friends or neighbors (47%), undergraduate advisors or professors (34%), physician acquaintances (31%), family doctors (23%), and physician relatives (18%). The physician acquaintance category was the chief source of discouragement (43%) followed by friend or neighbor (40%) and undergraduate advisor or professor (25%).

The leading reasons given by those who discouraged the study of medicine included long years of training (55%), cost of medical malpractice insurance (50%), excess government regulation (43%), poor life style (40%), diminished physician income in the future (39%), high cost of medical education (26%), and risk of exposure to the acquired immunodeficiency syndrome (22%) (Table II).

Seventy (22%) of the students thought that the reasons given by

TABLE I. Sources of Encouragement and Discouragement for Studying Medicine Among 314 First Year Medical Students

Source	Encouraged		Discouraged	
	Number	Percent	Number	Percent
Parents	183	58	50	16
Spouse	14	5	10	4
Family doctor	70	23	61	19
Physician relative	57	18	57	18
Physician acquaintance	96	31	135	43
Undergraduate	106	34	77	25
adviser or professor				
Other (friend, neighbor)	148	47	151	48

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TABLE II. Reasons Given to 314 First Year Medical Students by Those Who Discouraged the Study of Medicine

Reason	Number of Students	Percent of Students
Excess government regulation	134	43
Cost of medical malpractice insurance	157	50
Diminished physician income in the future	121	39
Poor life style	126	40
Long years of training	171	55
High cost of medical education	83	26
Risk of exposure to AIDS	70	22
Other	58	19

those who discouraged them were exaggerated while 128 (41%) thought they were not exaggerated. The remaining students did not know (20%) or else did not answer the question (17%).

DISCUSSION

Analysis of responses using the chi-square test of proportions showed no statistically significant differences according to when the decision to pursue medicine was made and the frequency of encouragement ($\chi^2 = 1.19, p = 0.76$) or discouragement ($\chi^2 = 5.75, p = 0.13$). A larger sample size, however, might have made this discrepancy statistically significant. There were no statistically significant differences between women and men ($\chi^2 = 0.01, p = 0.75$) and between minority students and others ($\chi^2 = 1.4, p = 0.24$). The majority of students surveyed are from middle-class backgrounds which strongly value upward mobility. Not surprisingly, few parents (16%) discouraged their children from studying medicine. The decision to choose medicine as a career was first made by 62% of the students before they entered college and this may have figured in their ability to withstand discouragement from various sources.

In the mid-1970s, Kutner and Brogan⁴ conducted a survey of men and women at two southern medical schools in order to assess their decision to enter medicine. They found that 19% of the women and 8% of the men had been discouraged by undergraduate male advisors or professors. In the current survey, 25% of students were discouraged by a similar group. However, physician acquaintances were the major source of discouragement for 43% of students, followed by friends or neighbors (40%).

Based on the data from this survey, it appears that both encouragement and discouragement come from a variety of sources including different types of physicians with whom students have contact. While parents prominently figure in encouraging students to study medicine, physician acquaintances, friends and neighbors, and undergraduate professors and advisors are leading sources of discouragement. Those who discourage often cite finan-

cially based reasons such as the cost of medical malpractice insurance, diminished physician income, and the high cost of medical education. Quality of life issues such as poor life style and long years of training are also prominently mentioned. Finally, excessive government regulation, which is perceived as both eroding the independence of a physician's work and having a negative impact on earning potential, is also prominently mentioned. Yet when all of the discouragement reasons are examined, it is clear that the ones related to economics and life style figure most prominently. There is some overlap between these two categories since long years of training have an impact on both life style and income.

The role of physicians in discouraging young people from studying medicine has been widely discussed as has the decreased appeal of medicine as a career.^{5,6} This current survey confirms the important role that physicians play in both encouraging and discouraging individuals from entering their profession. It is noteworthy that while 43% of students were discouraged by physician acquaintances, 31% were encouraged by them. This indicates that despite the many changes taking place in medical practice, there are a number of physicians who do not view them as so detrimental that they would discourage others from studying medicine.

The role of undergraduate advisors and professors in encouraging or discouraging students from studying medicine is one that has been documented, but clearly is one in need of closer study.⁴ It is significant that fully a quarter of students had been discouraged from studying medicine by those in this group while 34% had been encouraged (Table I). The full impact of such discouragement efforts by advisors and professors in deterring undergraduates from pursuing a medical career cannot be assessed by surveys of medical students. The latter represent those who, despite discouragement, have pursued the study of medicine anyway. A fuller picture of the impact of professors, advisors, and others on discouraging or encouraging the study of medicine can only be obtained through comprehensive surveys of undergraduates.

It is clear from this study that extrinsic values such as diminished economic rewards, increased economic costs, and life style compromises figure prominently among the reasons given by those who discourage young people from choosing medicine as a career.

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Abdominal mass and anasarca following treatment for lymphoma

CASE PRESENTATION

Richard J. Horner, MD (Attending Physician, Hematology/Oncology): A 77-year-old woman experienced rapid deterioration with onset of anasarca during chemotherapy for diffuse large cell lymphoma.

The patient's medical history was complex, with cold agglutinin disease five years before her final admission, surgical repair of pelvic outlet relaxation with vaginal hysterectomy, excision of a skin cancer from the left side of her nose, and chronic venous insufficiency complicated by left leg phlebitis.

Five and a half years prior to admission, the patient was found to have chronic anemia. Upper gastrointestinal endoscopy revealed a hiatal hernia and gastroesophageal reflux. Colonoscopy subsequently disclosed diverticular disease without evidence of local bleeding.

Eighteen months prior to admission, the patient had undergone right cataract extraction with intraocular lens implantation and had a complicated postoperative course.

Five months prior to admission, the patient was found to have an ulcerated mass on the posterior aspect of the left knee. She had experienced a five-pound weight loss. A chest film disclosed bilateral hilar adenopathy. Biopsy of the leg mass was reported to indicate small cell carcinoma, and the patient was referred to Mary Imogene Bassett Hospital for treatment. The patient had never smoked cigarettes.

Physical examination on referral disclosed no peripheral lymphadenopathy. The abdomen was protuberant without enlargement of liver or spleen. A 3 × 2-cm ulcerated excision site was present in the left popliteal fossa. The hemoglobin level was 11.5 g/dL; hematocrit, 33%; mean corpuscular volume (MCV), 94 fL; the white blood cell count was within normal limits; and the platelet count was 409,000/ μ L. Blood chemical values included a glucose level of 238 mg/dL; serum creatinine, 2.1 mg/dL; and a normal lactate dehydrogenase (LDH) level.

The chest film showed symmetric bilateral hilar lymph node enlargement, with bilateral pleural thickening; the heart was at the upper limits of normal in size; and a large hiatal hernia was present. Subsequent chest, abdominal, and pelvic computed tomographic (CT) scans showed mediastinal and bilateral hilar adenopathy without abnormality below the diaphragm. Bone and cranial CT scans

were normal. A bone marrow biopsy showed no evidence of tumor.

The original leg biopsy specimens were reviewed here. A histologic diagnosis of diffuse large-cell lymphoma was made and was supported by a positive stain for common leukocyte antigen. The pathologic stage was IV-A. The presence of chronic renal insufficiency prevented the patient's entry into an investigational treatment protocol; she was treated with cyclophosphamide, adriamycin, vincristine, and prednisone, in attenuated dosage because of her renal insufficiency and general debilitation.

After four courses of chemotherapy, the hilar and mediastinal adenopathy resolved. One month prior to admission, placement of an infusaport was required to permit intravenous access for additional chemotherapy.

During the two weeks prior to admission, however, the patient's condition rapidly deteriorated, with shortness of breath, watery diarrhea, increased abdominal protuberance, and marked peripheral edema. Shortly before admission, physical examination disclosed no peripheral lymphadenopathy; massive ascites, a large mass palpable in the upper abdomen, and marked pretibial edema were present. CT scan at that time disclosed marked ascites with possibly thickened mesentery. No retroperitoneal adenopathy or pericardial effusion was seen; the ovaries were not identified.

On admission to this hospital, urinalysis indicated urinary tract infection. The hematocrit was 26%; serum creatinine, 2.0 mg/dL; serum albumin, 2.2 g/dL; and serum LDH, 278 U/L (normal range 60–225 U/L). Repeated paracenteses yielded an exudative fluid with a protein content of 3.5 g/dL and a fluid LDH of 200 U/L. Three cytologic examinations of the fluid were negative for malignant neoplastic cells. The patient's anemia was treated with packed red blood cell transfusions. In view of her history of phlebitis, low-dose subcutaneous heparin treatment was instituted.

The patient persistently complained of shortness of breath, which was initially attributed to pulmonary compromise by her rapidly recurring ascites. However, this complaint did not improve after her repeated paracenteses, and by the sixth hospital day she was more dyspneic. At this time, an arterial blood gas determination, obtained with the patient breathing room air, revealed a pH of 7.38, a PCO₂ of 40 mm Hg, and a PO₂ of 41 mm Hg.

Later, on the sixth hospital day, the patient became confused; her serum potassium was found to be 5.9 millimols per liter, with a blood pH of 7.31. The patient's temperature rose to 38.5° C, and hallucinations devel-

Based on a clinicopathologic conference held at Mary Imogene Bassett Hospital, Cooperstown, NY, on November 28, 1989.

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oped. A urinary tract infection was treated with ceftazidime.

By the seventh hospital day, the patient's condition improved slightly, but on the following day she experienced shaking chills, persistent fever, and progressive hypoxemia. Despite more intensive oxygen therapy and treatment with gentamicin, hypotension developed over several hours, and she finally died.

RADIOLOGIC PRESENTATION

Lawrence Barnowsky, MD (Attending Radiologist): A CT scan taken five months prior to admission demonstrates extensive adenopathy in the mediastinum and hilar regions (Fig 1). Large nodes are seen in the paratracheal portion of the mediastinum, in the aortopulmonary window, and in the carinal area. A large bulky node or mass is seen in the region of the azygo-esophageal recess. A hiatal hernia is also identified. Two weeks later, a chest film confirms the hilar adenopathy.

One month prior to admission, a follow-up chest film shows that the hilar adenopathy has completely resolved. The hiatal hernia is still evident.

Shortly before admission, a CT scan was obtained at another institution without intravenous contrast (Fig 2). It shows a large amount of ascites surrounding the liver and spleen. Both kidneys are very small in size. The mesentery is surrounded by ascites, but there is also a great deal of thickening of the mesentery, either due to edema or from tumor infiltration. A loop of bowel in the region of the transverse colon appears to be narrowed. Ascites is present in the pelvis, but no ovarian mass is seen.

The final chest film taken shortly before death reveals an air-fluid level in the mediastinum from the patient's hiatal hernia. In addition, there are two crescentic air collections, one above the hiatal hernia and one just below the right hemidiaphragm, which may represent free air from a perforated viscus.

Dr Horner: My colleagues in the Division of Hematology have reviewed the subject of large cell lymphoma in detail on several occasions at various conferences during the past few months. Today I propose to review selected clinical aspects of the case, and then to discuss the place of the autopsy in current medical practice.

Turning to the clinical aspects first, this case illustrates



FIGURE 1. CT scan of the chest five months prior to final admission, disclosing mediastinal lymphadenopathy (arrows).



FIGURE 2. Abdominal CT scan on final admission showing ascites (arrow at left) with narrowing of the transverse colon (arrow at upper right).

the potential difficulties in making the diagnosis of large cell lymphoma. There is potential for confusion in the histopathologic differentiation between lymphoma, small cell carcinoma of lung, and undifferentiated carcinoma. Histochemical staining for common leukocyte antigen and studies for lymphocyte surface markers can be crucial in making a diagnosis of lymphoma. There was an important clinical clue in this case—the patient had no history of cigarette smoking, and for practical purposes the disease of small cell carcinoma of the lung does not occur in non smokers. In addition, symmetric hilar adenopathy would have been an unusual presentation for small cell carcinoma.

The second point I would like to emphasize is that this woman was treated with what is the classic regimen of chemotherapy for large cell lymphoma—cytoxan, vincristine, adriamycin, and prednisone—which is one of the first regimens capable of producing cure of advanced stage large cell lymphoma. A number of other regimens, most of them more complicated and more toxic, have since been developed, and we are participating in a multi-institutional cooperative-group clinical trial comparing the classic CHOP regimen with the newer m-BACOD, Pro-mace-Cytabom and MACOP-B regimens. This patient was ineligible for this important clinical trial because of her chronic renal insufficiency.

Rapid healing of the leg ulcer after chemotherapy was started suggested to us that it had not healed after the original biopsy because there was residual tumor in the ulcer bed. The chest film improved substantially, but after four cycles of chemotherapy, and despite a virtually normal chest film, the patient experienced the explosive appearance of progressive tumor, with an abdominal mass, ascites, and profound systemic symptoms.

The major alternative diagnoses, from our point of view, were recurrent rapidly progressive large cell lymphoma, versus the development of a second primary neoplasm. The second primary that we considered most likely was ovarian carcinoma, because of the clinical picture of massive ascites suggesting peritoneal carcinomatosis. We felt, however, that recurrent lymphoma was more likely, because of the explosive tumor progression, and because the dosages of chemotherapy had been attenuated, initially because of general debilitation and renal insufficiency, and later because of life threatening myelosuppression

produced by her initial course of chemotherapy.

There was no reason to suspect that the lymphoma chemotherapy had induced or influenced the course of a second malignancy.

The final clinical point that I would like to stress is that the dominant features of the patient's terminal illness were dyspnea and hypoxemia. We initially blamed this on her inability to take a deep breath because of massive ascites. But her dyspnea did not improve very much after paracenteses. The potential for thromboembolism was recognized in this patient, and she was receiving prophylactic, low dose subcutaneous heparin every 12 hours. However, on reviewing the chart for this pathologic conference, I could find no written comment by any of her physicians that suggested serious consideration of pulmonary embolism as a part of her terminal course. I anticipate, however, that one unexpected major finding in the autopsy could well be pulmonary embolism.

I would now like to discuss the current status of the autopsy in American medical practice. This conference was possible because the patient's family gave us permission to carry out a postmortem examination. We expect that the autopsy conducted by Dr Alpern will not only reveal the immediate cause of death, but also confirm or refute our impression that the patient's rapid deterioration in the last two weeks of life was caused by lymphoma that was refractory to chemotherapy.

The term "autopsy" is derived from the Greek, "to see for one's self."¹ Since antiquity, the autopsy has been a fundamental means of developing knowledge about disease. Modern pathology and clinical medicine have been intertwined in their development on a foundation of postmortem observations.² Since the 1940s, however, there has been a dramatic decline in the frequency of autopsies in the United States. In the 1940s, about 50% of all deceased patients were autopsied; in the 1970s this percentage had dropped to about 25%, and by the 1980s it was down to about 15%.²

In an era of high technology and advanced diagnostic capability, it is valuable to ask if the autopsy is still worthwhile and, if so, why it is in decline. Fortunately there is recent literature that helps answer these questions.

Landefeld et al² analyzed 233 autopsies carried out in a major teaching hospital affiliated with Harvard Medical School and at a suburban Boston community hospital. About three fourths of these autopsies represented complete examinations. The study compared premortem clinical impressions with postmortem findings. Treatable, unexpected major findings were discovered in about 11% of the autopsied cases. These findings were defined as medical conditions which, had they been diagnosed and treated, might have permitted continued survival. In addition, approximately 15% of the autopsied cases yielded unexpected major findings, the premortem diagnosis of which would not have changed the patient's course. Similar findings have emerged from numerous other studies.

What kinds of diagnoses were missed? Pulmonary embolism for a long time has been recognized as an entity that clinicians underdiagnose premortem. In this study, of the 24 pulmonary emboli present in this series of 233 autopsies, almost two thirds had been missed in antemortem evaluations. A significant number of systemic infections

had been missed, most of which were fungal infections occurring in immunocompromised patients. A small number of occult malignancies was discovered at autopsy.

The authors further analyzed the missed diagnoses from the point of view of why they had been missed. Sixty percent of the unexpected postmortem diagnoses had not been suspected premortem, and 40% were missed because test results had been "misleading, inconclusive, misinterpreted, and were unavailable before the patient died."

In an era in which we depend so heavily on technology, the latter finding is particularly chastening. We are tempted to believe that modern diagnostic technology progressively improves diagnostic accuracy. An earlier study by Goldman et al,³ which included a review of autopsy series from the 1960s, the 1970s, and the 1980s, at the same Harvard-affiliated teaching hospital, indicates that between 1960 and 1980 there was an enormous increase in the application of diagnostic radiology and imaging; nuclear scans, ultrasound examinations, and computer-assisted tomographic studies that were rarely used or did not exist in 1960 were heavily utilized by 1980 in the series of autopsied patients at that institution. Nevertheless, the percentage of major unexpected autopsy findings was virtually constant across the three eras studied. Modern diagnostic technology has made a undeniable impact on patient care, but has not eliminated diagnostic uncertainty.

In addition to its role as a method of monitoring diagnostic accuracy, the autopsy serves multiple other critical functions, as outlined by Nemetz et al.⁴ It continues to be a useful tool in the assessment of the efficacy and complications of medical and surgical treatments. It is part of the validation process of new diagnostic technologies. It is an important source of transplant tissue, particularly corneas. It is critical in the development of accurate epidemiologic data on which the development of public health policies can be rationally based. Finally, the autopsy is a means of informing, comforting, and reassuring the survivors of the deceased. The study by McPhee et al⁵ of attitudes toward autopsy among survivors of patients dying in a San Francisco teaching hospital suggested that most families had a clear understanding of the potential benefits of the autopsy.

The value of the autopsy is evident. Why, then, is it in decline? There are several identifiable reasons. One important reason is cost. At most centers, the cost of an autopsy is about \$1,000 (H. D. Alpern, personal communication, October 1989), and this is not reimbursed by insurers. In an era of decreasing reimbursement for patient care, when many hospitals are struggling to balance their budgets, there is no eagerness to take on non reimbursable activities and programs.

In 1971, the Joint Commission on the Accreditation of Hospitals (JCAH) eliminated the 20% autopsy rate as a minimum acceptable standard for hospital accreditation, concluding that no specific autopsy rate was appropriate for all hospitals.¹ This decision appears to have given momentum to a process already in motion. Professional disincentives appear to be a significant factor. Autopsies are not generally at the cutting edge of academic pathology, and the economic issues are clearly a disincentive to increasing autopsy frequency in the community hospital setting.¹

Finally, there is the matter of obtaining permission for autopsy. McPhee and his colleagues⁵ reported on the attitudes of survivors toward autopsy and on the process of obtaining autopsy permission. Through a questionnaire to family members of 102 patients who had died in a San Francisco teaching hospital, they made some disturbing observations. First, among the patients not undergoing autopsy, permission had not been requested in 45%. Requests for permission were made by the primary physician in less than half the cases. Day-to-day experience confirms the potential importance of the role of the primary physician at an extraordinarily difficult time for survivors. Finally, in many instances, family members were not provided with reasons for performing the autopsy or given reassurance regarding some frequent concerns, such as disfigurement of the body or delay of the funeral. A final point worthy of emphasis from the San Francisco experience was that more than a third of the families who did grant autopsy permission were never informed of the results. Obviously, the potential for providing useful information and comfort from the knowledge that care had been appropriate could not be realized without reporting autopsy findings to the appropriate family members.

With those comments and the realization that a discussion of corrective measures is beyond the scope of this presentation, I will ask Dr Alpern to review the autopsy findings. I anticipate that the patient was found to have significant pulmonary embolism and widespread intra-abdominal tumor, probably large cell lymphoma; and if there was a second primary tumor, it was most likely ovarian carcinoma.

CLINICAL DIAGNOSES

Extensive intra-abdominal tumor with ascites—probably large cell lymphoma.

Perhaps a new primary neoplasm, most probably ovarian carcinoma.

Pulmonary embolism.

PATHOLOGY PRESENTATION

Harlan D. Alpern, MD (Pathologist-in-Chief): Thank you, Dr Horner, for your useful and timely discussion of the continuing importance of the autopsy.

The skin biopsy performed during this patient's life demonstrated a dermal infiltrate composed of sheets of cells that are of medium size and are separate, one from the other. The nuclei were relatively large, with prominent, centrally located nucleoli. These are cytologically large lymphocytes. Staining for common leukocyte antigen, a membrane leukocyte antigen, was strongly positive (Fig 3), confirming that the neoplasm was a lymphoma, rather than a small cell anaplastic carcinoma.

At autopsy, there was no evidence of residual lymphoma. There was a tumor mass in the transverse colon (Fig 4), which had ulcerated, perforated, and infiltrated through the full thickness of the bowel wall into the mesenteric fat and omentum. On histologic evaluation, this tumor was primarily adenocarcinoma, composed of glands of moderate degree of differentiation (Fig 5), which infiltrated through the submucosa and the muscularis propria, into the serosa and adjacent fat. In most areas, the glands were closely packed and of variable size. In

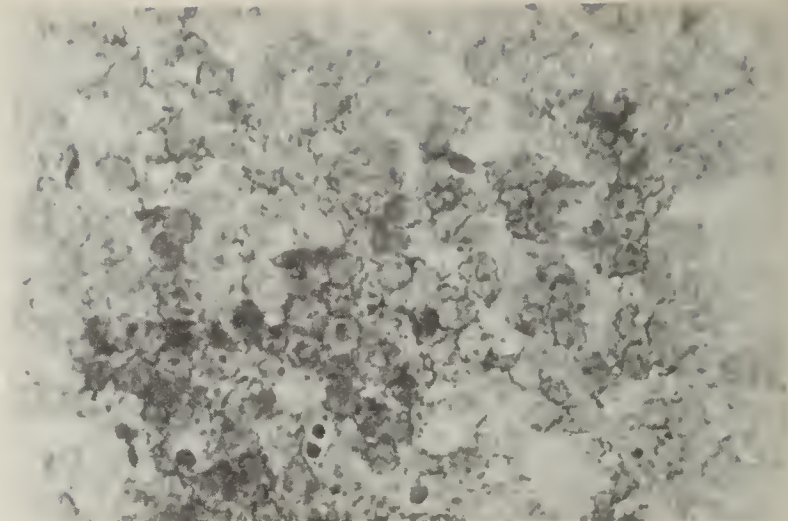


FIGURE 3. Common leukocyte antigen deposited on surface membranes of large neoplastic lymphocytes in dermis (common leukocyte antigen; original magnification $\times 400$).

some areas, there was abundant mucin production, with tumor cells lining lakes of mucin and lying free within mucin. Focally, there was undifferentiated carcinoma in which the cells did not form glands but formed cords and small nests within which no mucin could be demonstrated on histochemical analysis. Neither did histochemical study demonstrate carcinoid differentiation.

In the liver, there was evidence of a metastasis, in the form of a single 8-mm white nodule. This lesion was adenocarcinoma, histologically similar to the adenocarcinoma in the colon. The adjacent liver demonstrated marked fatty change, with large lipid vacuoles within most hepatocytes. The gall bladder contained multiple, irregularly shaped brown stones, and there was a mucocele of the gall bladder. Along the peritoneal surfaces including the splenic surface, there was evidence of metastatic colon carcinoma.

In the lung was a small tumor, 1 mm in diameter, which was a minute carcinoid tumor composed of neuroendocrine cells. The ovaries were of normal size for the patient's age. There was focal metastatic carcinoma from the colon in lymphatics of the ovary. The cellularity of the bone marrow was normal and showed evidence of recovery from chemotherapy; there was no evidence of neoplasm in the bone marrow. The kidneys were arterionephrosclerotic.

The mediastinal lymph nodes were enlarged, measuring

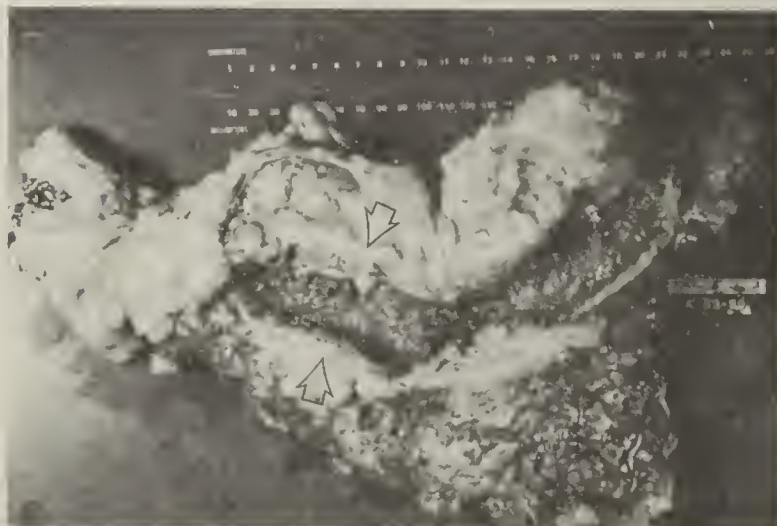


FIGURE 4. Carcinoma of transverse colon, invasive into mesentery and omentum (arrows).

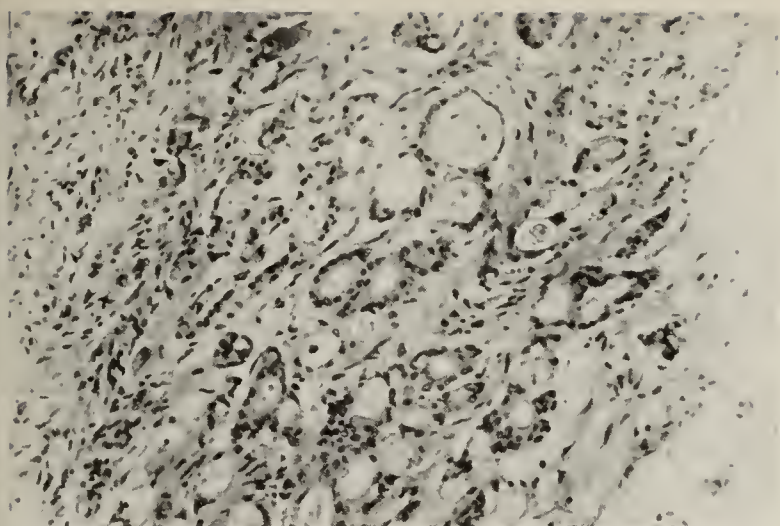


FIGURE 5. Adenocarcinoma, moderately differentiated, in the transverse colon (hematoxylin-eosin stain; original magnification $\times 100$).

up to 4 cm in maximum dimension. These lymph nodes demonstrated no evidence of lymphoma or metastatic carcinoma. There were, however, confluent hyalinized granulomata, spherical nodules that were densely hyalinized and contained multinucleated giant cells (Fig 6).

Stains for acid-fast bacteria and for fungi were negative. Most probably these granulomata represented burned-out sarcoidosis.

In the right atrium, there was adherent mural thrombi; in the right lung there were pulmonary emboli in large branches of the right pulmonary artery. Secondary to the emboli, the right lower lobe was the site of infarction, with obliteration of pulmonary parenchymal architecture by hemorrhage and necrosis.

In summary, the postmortem examination demonstrated that this 77-year-old woman died as a consequence of carcinoma of the colon. The carcinoma arose in the transverse colon, exhibited extensive local invasion, and had metastasized. The final event leading to her death was a pulmonary embolus from mural thrombi in the right atrium with infarction of the right lower lobe.

This case of an unsuspected second primary neoplasm, as well as a clinically unrecognized final event, that is, the pulmonary embolism and infarction, is an excellent illustration of the continuing importance of the autopsy.

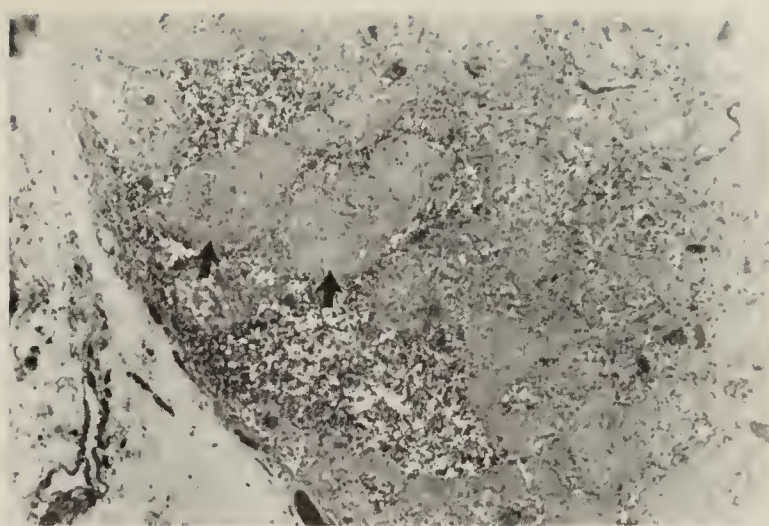


FIGURE 6. Hyalinized granulomata compatible with "burned-out" sarcoidosis in mediastinal lymph node (arrows) (hematoxylin-eosin stain; original magnification $\times 40$).

ANATOMIC DIAGNOSES

Adenocarcinoma in the transverse colon, with invasion of intestinal mesentery and omentum with metastases to liver, peritoneum, and ovary.

Organized mural thrombus in the right atrium, with right pulmonary emboli and right lower lobe hemorrhagic infarction.

Coronary atherosclerosis, focally marked, in heart.

Granulomatous lymphadenitis, hyalinized, consistent with "burned-out" sarcoidosis.

Marked fatty change in the liver.

Small tumor in the upper lobe of the left lung.

Cholecystolithiasis, with mucocele of the gallbladder.

Arterionephrosclerosis of the kidneys.

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Physicians and national health insurance: Some economic factors

THOMAS P. WEIL, PhD

A United States health care plan that ensures patients at least universal access, if not universal insurance, is once again high on the nation's agenda.¹ As various approaches to modify our current pluralistic system are studied, it will be imperative for our health policy leadership to consider the fairness of access, the value for money spent, and the quality of the patient care offered by physicians, hospitals, and other health care providers.

Recent publications have called for developing a US health care policy;² analyzed the British National Health Service and the Canadian national health insurance (NHI) plan, and their potential applicability to the current US scene³⁻⁶; and proposed the broad outlines of a US NHI plan.⁷⁻⁸ This article provides somewhat different perspectives by focusing primarily on fiscal concerns that will lead the United States first to universal access and then to NHI earlier than previously anticipated; and on how various cost containment measures will shape such a plan, thereby affecting the practice of medicine in the future.

PRESENT FISCAL FORCES

As a number of congressional⁹ and other related groups continue to study NHI in the 1990s, they will undoubtedly shift their focus away from institutional long term care (9.0% of the nation's medical care costs). This is because of the increasing realization that such coverage on an insured mandatory entitlement basis (ie, without a means test) has yet to be either fiscally affordable or politically feasible in any Western industrialized nation.¹⁰ The United States Chamber of Commerce; the National Association of Manufacturers; and groups representing physicians, hospitals, health insurers, and advocates for children recently joined together in a successful campaign, as part of the October 1990 US deficit budget resolution, to expand Medicaid. This new provision will start to cover all poor children through the age of 18. This might suggest that universal access for the over 30.0 million employed and their dependents who are uninsured will be enacted first.

Meanwhile, an additional number of business leaders are becoming supportive of NHI since employers' health insurance costs are increasing at the rate of 14-15% per annum. Currently, the most frequent issue at union nego-

tiations is who will pay for the rising costs of hospital and physician services. Managed care plans, including health maintenance organizations (HMOs) with full-time salaried physicians, were once considered the prime option for containing costs in a competitive environment. However, their premiums have been increasing at rates similar to more conventional coverage and they are no longer perceived as bargains.¹¹ Moreover, many Fortune 500 companies have obtained the services of employees in part by promising them health benefits after retirement. The present value of such liabilities that have to be added to the balance sheets of the 100 largest companies in 1993 exceeds \$227 billion and is inflating at the rate of 10% per year.

The nation's business community has become even more hesitant about cross-subsidizing the shortfalls in Medicare and Medicaid as additional federal and state cutbacks are implemented (as proposed in October 1990). Meanwhile, the current 63.0 million who are underinsured sometime during the year grow in number,¹² and an increase in hospital foreclosures can be anticipated, particularly among the inner city facilities that historically have federally insured or similar mortgages. The nation's acute care facilities, which are experiencing their weakest bottom lines, will seek an expeditious solution that falls far short of nationalizing the industry (ie, British National Health Service). Universal access would provide an opportunity for government to bail out these hospital mortgages without a change in ownership and without significant public subsidy.

What is so interesting about this current NHI debate is that there are many elected officials and physicians who believe this country can ill afford an NHI program. Yet there are at least an equal number of leaders from other sectors of our society who think that a civilized nation cannot survive without equal access and equity in the provision of its health care services. The business community, the aged, the uninsured or underinsured, and some health care providers have formed an unusual political coalition to pressure members of Congress for at least equal access, if not universal insurance, which for the fiscal reasons outlined above could very well occur in the early 1990s.

VIABILITY OF UNIVERSAL ACCESS WITHOUT UNIVERSAL INSURANCE

The American Medical Association¹ (AMA) has made a proposal that would expand eligibility and coverage un-

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der Medicaid to ensure universal access for those below the poverty line. For uninsured persons who are above the line, it would create "state health risk pools"¹³ with a voucher system to purchase care. Enthoven and Kronick's⁷ consumer choice plan, a somewhat different approach, proposes universal insurance coverage whereby employers would provide minimum benefits for their employees. Each state would have a "public sponsor" to guarantee coverage of the self-employed and others not so covered. These sponsors would also encourage choice for all the insured among rival managed care plans as a better route to cost containment rather than through price controls.

In both the AMA¹ and Enthoven and Kronick⁷ proposals, the current pluralistic system (multi- versus single payor) without mandatory assignment (acceptance of the assigned fee as total payment) for the middle and higher income private patient would continue "because it would present consumers with a choice among health plans and an opportunity to exercise cost-quality judgments." The issues of single versus multiple third party payors, and mandatory assignment versus allowable extra billing, are possibly as crucial decisions as any other in discussing the fiscal implementation of any future US universal access or NHI plan.

The United States has evolved a complex prepayment system of multiple organizations, not-for-profit and commercial carriers competing for enrollees, with the more onerous risks covered by various public programs. An NHI plan could be so designed to mandate premium payments to private insurance carriers, thereby keeping the current multiple payor system intact. An alternative would be to establish a single payor of health care costs, at the state or federal level, to collect taxes, social security contributions, and employer/employee premiums in one fund, and use these monies to pay health care providers.

It would be difficult to provide universal access without universal insurance partly because the United States, with its multiple payors of health care and allowable extra billing, has suffered a relentless rise in health care costs. Canada, in contrast, with a single payor and mandatory assignment, has been more successful at cost control while providing comprehensive coverage to its entire population.^{4,14} Great Britain and Japan have done the same.¹⁵ In these nations, the overall quality of care, as demonstrated in gross measures of health status, equals or exceeds that of the United States. France, West Germany, and the Netherlands, which have health systems that more closely approximate the concept of a single payor rather than multiple payors of care, have also shown a greater ability than the United States to control costs without clear-cut negative effects on quality.

In providing universal access without universal insurance, it is also worrisome that 37 million uninsured, eligible Medicaid recipients, and the aged with Medicare deductibles and coinsurance, could well seek newly mandated and potentially available physician and hospital services. This would force an untenable fiscal outcome of increased cross-subsidization from the private sector as the federal and state governments hesitate to levy additional taxes—always unpopular—to pay for these services.

If an AMA¹ type universal access approach without universal insurance could be subsidized by public funds,

why not simply raise Medicaid eligibility levels and broaden the benefits? This would utilize an already existing program and would pay providers closer to usual, customary, and reasonable fees for physicians and per diem/per discharge payments to hospitals. New York State's Medicaid program, whose eligibility criteria are among the most liberal in the nation, is certainly not a model for others to follow. Nor is the controversial guaranteed health insurance program in the Commonwealth of Massachusetts. The funds to pay for universal coverage without universal insurance have to come from somewhere. Controlling rising costs that are sometimes driven up by new and improved technology continues to be a problem that could make compulsory prepayment necessary, although still unattractive.

As we look toward the potential implementation of a plan of universal access but no compulsory insurance, state health services commissions would probably be established to administer these new benefits. Although responsive to local interests, they would share a patchwork quality common to other national social programs, many of the risks of creating inequalities in access and benefits, and inefficiencies in administration. Since 1965 the Medicaid program has taught us a good deal about potential weaknesses in allowing the state to determine benefits and eligibility standards and administer complex programs. If a program is universal rather than exclusively for the indigent; administratively relatively simple, unlike the complex and fiscally restrictive Medicaid programs; and has adequate federal funding, then many states might administer an NHI program very well.¹⁶

The overall evidence suggests that to avoid a crippling inflation of health care costs, any NHI plan that provides universal coverage should be organized around a single payor of health care, or a coordinated group of payors, and that quality of care need not suffer under such an approach. While single payor nations ration patient care by imposing budgetary restrictions, the United States rations much of its services by failing to adequately provide universal access.¹⁷⁻¹⁹ The latter method of rationing may seem more equitable, but it is highly unlikely that in the long term, broad coverage would be fiscally viable without a single-payor, universal insurance approach, primarily because consumer expectations and provider-induced demand would continue to outstrip available private and public resources.

IMPACT OF NHI ON PHYSICIANS

The new resource based relative value scale (RBRVS) Medicare fee schedule, to be phased in over a five-year period starting in 1992, is under attack by many medical and surgical subspecialists as well as hospital based physicians, although at the outset it will have modest negative impacts on the incomes of most of them. What should be of far greater concern is expanding the RBRVS approach to the entire insured population, which many believe will eventually happen anyway. Since it is unlikely that physicians under an NHI program will be paid an annual salary adjusted for specialty, experience, location, and other factors, or on a capitated basis, the Medicare relative value or resource based approach becomes a critical historical precedent. This is because it will be the linchpin in the physi-

cian reimbursement methodology, first with universal access and then later, if enacted separately, for compulsory insurance.

Under these circumstances, to gain the physicians' political acceptance of an NHI plan, they will have to be reimbursed under a universal and comprehensive, public medical insurance program. This would be according to a fee-for-service schedule based on the then existing Medicare and modified and expanded relative value units, negotiated periodically between the professional associations and the state health services commission. In the early years under NHI, physicians will probably be allowed to "extra bill." This provision would be eliminated once the NHI principle has been firmly established, in order to reduce the nation's overall health care expenditures and to portray a more egalitarian image for the program.

As a global target is set for physicians' fees and related services, first on a national and then on a state-by-state basis, and there is an agreed-upon state physician fee schedule, large increases above projected volumes because of any provider-induced demand will result in a reduction of the fees per unit of service the following year. An obvious concern is that this reimbursement system would encourage quick and frequent visits, and would penalize practitioners who choose not to practice that way.

Another major question surrounding the impact of NHI on physicians is what benefit coverage and level of quality can realistically be provided under the NHI plan. Then there is the most impossible task of finding some middle ground between an attempt to cover virtually everything and the current reality in which almost nothing is covered. This is a topic recently discussed by Welch²⁰ under the intriguing title, "Health Care Tickets for the Uninsured: First Class, Coach, or Standby?" There has been a reluctance among health policy experts to admit there has been a historic rationing or prioritizing of health resources.²¹ Key criteria in determining who is more likely to receive optimal care are often based on a patient's insurance coverage or ability to pay any other out-of-pocket expenses.²²

To ensure these broader benefits, a few physicians will recommend managed care plans that could be held at financial risk for providing mandated care within the total fiscal resources received from the payor. This approach has obvious conceptual cost-containment advantages as demonstrated by some HMOs, and includes financial incentives to their physicians to reduce unnecessary hospitalization and expensive procedures, and to minimize administrative costs by simplifying billing and collection systems.²³⁻²⁵ But any capitated payment system, including the HMO, has inherent problems. These include the financial incentives to physicians for providing too little care; the bureaucratic and/or financial constraints that discourage provider utilization; and incentives to market enrollment primarily to low utilization populations, thereby increasing the ability to contain premium costs.^{11,26} For these reasons, managed care programs are unlikely to play a major role in any future NHI development.

As organized medicine has been historically among the strongest opponents of NHI,²⁷ it is somewhat ironic that with universal fee-for-service physician coverage, doctors would have a free choice of practice settings and the physi-

cian-patient relationships would no longer be constrained by a patient's inability to pay.¹⁴ Although universal coverage would solve a major problem in medical services by eliminating financial barriers to care, it could affect physicians in a number of negative ways.

First, state health services commissions, by controlling and adjusting specific fees downward, could succeed in providing almost all the community's high technology within the hospital's global budget, thereby eliminating some profitable ancillary revenues from physicians' offices. Doctors may even find themselves selling some of the office based technology to their community hospitals. Second, these state health services commissions will eventually also include, if possible within the hospital's global budgets, the professional services for pathology, radiology, anesthesiology, and other hospital based physicians, or these will be negotiated on a fee-for-service basis. In either case, this will have a significant negative impact on these physicians' professional incomes, particularly since any other practice revenues outside the acute care facility will be carefully monitored.

And finally, the fiscal incentive for hospitals under a global budget approach would appear to be to maintain a high average daily census, suggesting more custodial-type patients in acute beds and a potential difficulty in scheduling elective surgery admissions in the future. The preferred long term care facilities have long waiting lists and under NHI there would be no out-of-pocket expense for an acute care stay. Therefore, the family might pressure the physician and the hospital for the aged patient to remain in that setting until a preferred nursing home bed finally becomes available.

A more obvious source of revenue to deliver needed care rather than to lower physician incomes as outlined above would be to eliminate the 1,500 private health insurers in the United States. They now consume about 8% of our current health care expenditure, whereas both Medicaid and the Canadian national insurance program have overhead costs of 2% to 3%. This would generate a savings of \$62.0 billion (1989).²⁸ Reducing the number of payors to one or to a small coordinated group would reduce physicians' need to employ office personnel to handle billing and collections. In United States private practice, physicians waste countless hours on billing and bureaucracy, while the Canadian fee-for-service practice with negotiated fee schedules and mandatory assignment has reduced physicians' overhead.²⁹ In addition, it has been proven to be compatible with total health care cost containment, adequate (not superior) incomes for physicians, and a high level of access to and satisfaction with care on the part of the patient.³⁰

CONCLUSIONS

Political support for purely market oriented health care reforms during the Reagan and Bush administrations has been weakened by at least two persistent problems. One is the almost complete failure of competitive strategies to stem rising health care costs. The other is the increasingly visible problems of restricted access and uncompensated physician and hospital costs that result from the growing number of those who are uninsured and underinsured. Recognition of these issues may represent the limits of political

and fiscal consensus to this point, but with each of the major health care political camps adopting a more pragmatic perspective toward universal access reform, realignments are possible, and the prospects of enacting a major step toward an NHI program seem more likely each year.

The forthcoming RBRVS Medicare physicians' fee schedule may have some parallels to the hospitals' experience with the prospective payment system diagnosis related groups (DRG) methodology, particularly in the sense of lowering reimbursement to providers and developing even more bureaucracy with its added paperwork. The RBRVS methodology, if used by virtually all third party payors, would clearly affect most physicians' incomes, the amount depending upon the discipline, with the medical and surgical subspecialties most adversely impacted. Thereafter, a policy of expenditure targets or volume controls,³¹ an approach similar to many NHI proposals to address the then predicted rapid growth in the number and intensity of services as a direct reaction to RBRVS, could well be implemented.

The more critical NHI arguments for physicians possibly center on whether or not universal access without universal insurance can be provided, and whether or not single payor or mandatory assignment is required to ensure equity, cost containment, and quality of patient care. Irrespective of some conceptual and fiscal arguments, universal insurance that mandates physician, hospital, and prepayment and administrative expenses comprising roughly 70% of the medical care dollar expenditure has so much more political appeal than universal access alone, since it benefits the aged, the uninsured, and underinsured, as well as many employers. There might be an interval of several years in which the United States will have universal access without universal insurance. Undoubtedly it will not be long, however, before the issues related to a pluralistic versus a single payor system, and mandatory versus allowable extra billing, are then vigorously argued.

There will be more access and equity for the traditional indigent and medically indigent patient, and patient-physician relationships will be strengthened since almost all financial concerns will be eliminated. A number of more subtle changes will also occur. The nation's percentage of its gross national product (GNP) for health care will be gradually reduced by slowing down the introduction of new technology as evidenced by the Canadian experience;³² total (not individual patient) volumes and cost of services will be controlled;³³ and physical plant and equipment replacement and renovation will be delayed. As it becomes increasingly difficult to sustain the nation's present overall quality of care (although less of it may be substandard), as our position of preeminence in medical science breakthroughs starts to waver, the nation's morbidity and mortality statistics will slowly improve as more access and equity in the health care system is implemented.

As NHI evolves, hospitals will eliminate their marketing, joint ventures, and almost all their billing and collection staffs, and could use these monies to provide more direct patient care since the current bottom line mentality will be superseded under NHI with a thrust toward more community health services. Meanwhile, physicians will spend more time treating patients and will need to respond to far fewer external inquiries relating to managed care.

These more subtle changes may be palatable, but of far greater concern is whether the federal and state governments can recruit a staff of qualified public servants who can sufficiently engender trust among physicians, hospitals, and other providers to implement NHI effectively and efficiently. No one has ever said that NHI will be better than our current pluralistic system. It certainly could be quite negative in terms of new external controls and in reduction of current physician incomes.

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The memoirs of Joseph Isaac Bluestone, MD

NAOMI R. BLUESTONE, MD, MPH

Almost 60 years ago, Dr Joseph Isaac Bluestone, widowed and living with the youngest of his eight children, sat down to write his memoirs. These memoirs, translated in 1934 by his son Harry Bluestone, have been published only in excerpt, in 1976 and 1977.^{1,2} Although articulate and literate in a number of languages, Bluestone wrote in Yiddish, the tongue of his mother culture. While these memoirs are of interest primarily to historians of early American Zionism and Jewish education, to which he had devoted the lion's share of his intellectual endeavors, they speak cogently to those celebrating the centennials of a number of New York's social and medical institutions. Like many men whose broad range of interests led them into several simultaneous careers, Bluestone elected to enter the profession of medicine, which he perceived as a communal endeavor and responsibility, part and parcel of his all-abiding interest in the welfare of his Jewish community. Bluestone's memories of his medical school training; his years in practice on the Lower East Side, including both the deprivations and triumphs of a poor "lodge" physician, and his growing prosperity; and his role in the establishment of a community hospital for his people are written with the acerbic wit and sense of humor for which he was well known. In this essay, selected impressions of a participant observer of the medical care scene on the Lower East Side at the turn of the 20th century are presented.

THE CHILDHOOD EXPERIENCE

Bluestone was born on February 10, 1860, in Kalwarya, Lithuania, which was at that time a prosperous, virtually all-Jewish town of over 6,500 souls. Kalwarya went into decline in the ensuing years, and was completely annihilated by the Nazis after their occupation on June 22, 1941.³ His father was an Orthodox Jew of intellectual pedigree, but a poor man whose dowry and livelihood had been a one room wooden house with a thatched roof, surrounded by orchards and cornfields. Bluestone, like many immigrants to the United States, was raised a country lad, with animals in the basement, chickens in the garret, and an education marked by all-night candle-lit study sessions, in which he pored over the holy books of his religion. By the age of 15, despite his genuine love for the life of religious learning, he joined the Enlightenment, convinced that there was no incompatibility between his heritage and secular learning. He resolved upon a career in medicine.

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Bluestone gives no hint in his memoirs of a perceived connection between the catastrophic illnesses which plagued his childhood, and his choice of career. But his narrative reflects early experiences which could well explain his interest in healing. He endured the sequelae of impediments to prompt access to medical care, inadequate control of pain and suffering, and the loss of supportive loved ones at a time of crisis. All of these may have sensitized him in ways that would have been clear to his contemporary, Sigmund Freud. Consider, for example, the following early notation:

During my youth, I suffered not only the diseases of childhood but of maturity as well, such as cholera, typhoid and pneumonia. My grandmother resorted to all sorts of peculiar remedies and preventive measures, such as measuring graves with threads which were later used as wicks for candles, pouring out wax, and carrying me to the corpse of my great-aunt Menucha, the wife of my great-uncle, Israel Menuchas, prior to the final preparation for burial. My grandmother raised the sheet that covered the cadaver and with the cold dead hand of my aunt, patted my entire body. All of these were of no avail, however, and the Angel of Death with his thousand eyes sought me as with candle light. He utilized every clever trick to reach me, and he surely would have succeeded were it not for the kind advice my teacher gave that my original name be changed. This certainly confused him, and he always had to withdraw in chagrin. I can imagine how all the demons stuck out their tongues at this devil . . .

(Earlier in his narrative, Bluestone mentions a beloved teacher who at the time of his illness "travelled a long distance to visit me and teach me. When I grew worse, he advised my father to add another name to mine, so that when the Angel of Death would look for the soul of Isaac Ben Chaim, he would not find it. Henceforth I was to be known as Joseph Isaac. From that time on I carried both names, and so the Angel of Death was ignominiously fooled. It seems as if his sight is keener than his intelligence . . .")

At the age of 12, Bluestone was sent to spend the Jewish festival of Shevuoth at the home of his mother's aunt in another village.

I accompanied a Gentile lad into the woods to chop some logs for firewood. We then went to the stable to water the horses. I asked permission to ride one of them for the experience. On the way to the watering place the horse bolted and threw me to the ground, fracturing my left thigh bone. My uncle carried me in his arms to his home. It was too late to take me to my parents, so I had to remain over the holidays in the village in tremendous pain . . . Immediately after the holidays, I was covered up with blankets and placed in a wagon on a mattress. The trek home was a



FIGURE 1. Joseph Isaac Bluestone, MD, in 1926, Denver, Colorado, age 66.

most painful experience. One can imagine the anguish of my parents when they saw the condition I was in and learned of my experience. In our city there lived a man named Louis the Smith, who was considered an expert bone setter. He attended me and on the third day, when he saw that the leg was growing crooked, he reset it correctly. Naturally, the pain was indescribable. I remained in bed a few months, then used crutches for a long time. At the outset my family said, "This also is for the good. Perhaps this will free you from conscription or military service, since lameness is a cause for exemption." Such a miracle did not happen, however. I became fully cured . . .

Level-headedness and a capacity to view life with his eyes wide open, characteristics which were to stand him in good stead in his later life, manifested themselves quite early.

In those days a cholera epidemic raged and masses died. There wasn't a house that did not contain a corpse. I was never afraid of the dead, and I was always accustomed to going home alone at night when school was over. Once on my late journey home, not far from the cemetery, I saw a white object jumping up and down, up and down, as if from the graveyard, again and again, nearer and nearer to me. I stood still waiting to see what it was. When it came close to me I recognized that it was a white hen, the feet of which were tied. Most probably a farmer had lost the hen while riding. I picked her up and brought her home. My parents were amazed at my courage, which was due to the fact that I never believed in superstition.

TRANSITION TO THE GOLDEN LAND

By his 18th year, having escaped the clutches of a number of marriage brokers, Bluestone began to plan for his professional future. His father had preceded him to the United States, and in 1880 was able to send enough money to bring over the entire family. On November 13, 1880, Bluestone set sail from Liverpool on the S.S. Victoria, considered to be one of the finest liners of her day, being half steam and half sail. He recounts at length and in detail the harrowing crossing, during which the ship's rudder broke, causing her to drift helplessly, at the mercy of

heavy storms and high seas, for several weeks. When the ship was rescued long after all hope for her had been lost, the event made the front page of the *New York Times* (December 10, 1880).⁴ The steerage passengers, who had been given no assistance and were close to starvation, endured unspeakable suffering, but Bluestone noted that the presence of a good companion with whom he could discuss Talmud made the voyage bearable. Years later, when he received his medical diploma on the stage of the new Metropolitan Opera House (1890), he likened his relief to that he experienced when his ship reached safe harbor in the port of New York.

In 1882, Bluestone was married to the daughter of his father's cousin Peter, Sarah Rachel Bluestone, herself a "Yankee" having been brought here as a child of two in 1864 and therefore raised as an American. It was by his account a happy marriage, and it was she who consistently supported him financially and spiritually, so that he could put his medical studies and his communal work foremost in his thoughts. To support his growing family, he initially had to put aside thoughts of a career, and went to work as a customer peddler, then as the proprietor of a dry goods store and a fur operator, all to no avail. He was not cut out for business, and experienced repeated failures and disappointments.

Although not the subject of this essay, the years 1880–1886 were spent not only in eking out a living, but in communal work. Bluestone labored unceasingly, organizing the Jewish community in Zionist activity, founding and editing a journal in support thereof, establishing fraternal orders, building charitable organizations (to clothe the orphan children and needy, for example), and promoting Hebrew education. (He even found time to write a volume of Hebrew poetry, published in 1930 in Palestine.⁵) The social connections he made during these undertakings were later put to good use in the service of his growing practice, although he was careful never to take financial advantage of them.

MEDICAL STUDENT DAYS

After much thought and consultation, since he was well aware of the vast discrepancies in the quality of medical schools pervasive at the time, Bluestone enrolled at the University Medical College in 1886. His description of the medical school years of the late 1880s, which can only be briefly excerpted here, is of great interest. It was an era of transition in medicine; a host of marginal and substandard medical schools were soon to be closed.⁶ (Only the confidential advice of a senior Jewish physician had saved him from enrolling at the already doomed Eclectic Medical College.) The dominant note which emerges is that the pressure, competition, and anxiety which many of today's physicians remember as their scholastic heritage were very much in evidence 100 years ago.

It was common practice in the college for students to select and keep the same seats throughout the year. No one was permitted to occupy any one else's seat even though it was vacant. This practice was disclosed to me by someone in the office. It was also common practice for students to come very early and stand on line in order to select for themselves the best seats in the lecture hall. On the first day of college, I arose before dawn and went to the school very early in the morning. I was not aware that many

students hired "strong arm" men who, by mere exhibitions of strength, could obtain the best seats in the hall. These men would enter and paste a slip with a student's name on the seat he was to occupy. The students then retained these seats for the remainder of the year. When I arrived, I found a line of men who probably had spent the night there. At 9:00 AM sharp, when the doors opened, the pushing began in earnest. The result was that I was forced to find a seat in the rear of the lecture hall. When I looked at the blackboard, I saw a notice to the effect that thereafter anyone could occupy any seat he desired. The common practice had been abolished

Those were lean years for immigrants fortunate enough to attend medical school, even those, like Bluestone, who did so on scholarship.

God knows that I endured, during my years at college, far more than I ever anticipated. I walked to school daily because I had no money for carfare. I took along a slice of dried bread with herring (if there was any in the house) and at lunch time I hid in a corner where I ate my dinner in solitude. My wife's relatives gave me no help of any kind. All I received from them was aggravation and fault-finding because I neglected the economic welfare of my family in order that I might satisfy my vanity and study a profession . . . my wife suffered much more from their accusations. Whenever I arrived at home and found my wife in tears, all I had to do was ask, "Who came from Paterson today?"

. . . The winter of 1887-1888 was a sad one for me. There was very little money for such necessities as coal for the house. On the twelfth of March, America's most severe blizzard raged. Snow began falling in the evening and on the next morning it had reached the third floor. The windows of our rooms, blocked by a wall of snow, became pitch dark. When I went to the grocery store to fetch a pail of coal, I had to cross a narrow lane, with hardly enough room for one person to pass the other. In those days, I was accustomed to walking to college because of lack of necessary fare. One can imagine how great was the risk and the suffering when I had to walk through snowdrifts to reach my destination two miles from home. [Note: The University Medical College at that time was on 26th Street.]

The year 1889-1890 was the worst year of my life. It was the last of my studies. I found it necessary to review all subjects. (I had already passed anatomy, physiology, chemistry and physics). I had to attend various clinics in medicine and surgery, and had to go from place to place in a constant state of hunger. My wife, who was an expectant mother again, ate dinners at my parents' home . . . I was forced to economize on time for my lessons (because of communal activities and writing copy for the journal). I was broken in health. Only optimism and trust in the future supported and strengthened me.

Four children were born to Bluestone and his wife between 1883 and 1889. The first was a son: ". . . My son, Aaron Harry, aged 15 months, suddenly developed diphtheritic croup. Immediate operation was advised by the attending physician. I took him to Mt. Sinai Hospital, where he died within two days after the operation. So we were left alone, I and my wife, poor and desolate."

Bluestone's wife encouraged him to put in an extra year of study, not required by the college, which he did. Eventually, that, too, came to a welcome end.

I took my final examinations and one week later the results were to be made known. That week was one of torture and hell; the days and the hours were counted until the Day of Judgment. I then went to the college to hear the decision. I met a Jewish classmate with a package under his arm. "What are you carrying, may I ask?" I naively questioned him. "Why, what do you mean?" he said, with great confidence. "Why, a high hat, of course!" In those

days, it was the custom for physicians (and cabdrivers, by way of contrast) to wear high hats. This fellow prepared himself so that, upon hearing the glad tidings, he should be able to dress as befitted a man of his dignity. I considered my old derby and my heart beat rapidly. Who knows? Possibly fate had ordained that I should wear my old hat another year? Suddenly I heard my name. I had passed the examinations creditably and earned the MD degree! I could hardly believe my ears. A doctor in a derby, and an old one at that! The student with the package waited and waited but in vain. His name was not called

I raced home to notify my family that I was not just an ordinary mortal any more. Hereafter I was to wear a high hat. But a few friends of mine anticipated me and broke the news to my family. When I reached home the rejoicing was endless and indescribable. Even my in-laws became friendlier.

In March, 1890, in the newly erected Metropolitan Opera House, I was presented with my diploma. I registered it at the Board of Health, and the County Clerk's office. I then became a full-fledged physician with an empty pocket and a hungry stomach. Now I really had to begin worrying how to support my wife and three daughters. It was always my fervent hope that my wife would give birth to a son, but I had no choice in the matter. Possibly, being a physician, I would be more fortunate in the future. A Jew must never lose hope

Bluestone was granted his request on Saturday, December 26, 1891, with the birth of his son Ephraim Michael Bluestone. (Dr E. M. Bluestone became the first medical director of the Hadassah Medical Organization in Palestine and was for many years director of Montefiore Hospital in the Bronx.) Three more sons followed. Bluestone was proud of his brood, who followed in his medical footsteps. "I have four daughters," he once boasted. "Three of them married doctors, and one of them married a Rabbi. Now I have three sons-in-law who can make me well for nothing, and one son-in-law who can make me good for nothing!"

A NEW PRACTITIONER IN THE COMMUNITY

Following his graduation from medical school, Bluestone combined two all-abiding interests. In the decade following his arrival in this country, a great influx of immigrants swelled the population of the Lower East Side. This massive migration has been well chronicled elsewhere.⁷ Bluestone took note of this and the growing need for hospital services to serve this exceptionally needy population. He was particularly interested in seeing to it that Jews should be cared for in a way which permitted them to observe their customs and traditions, eat Kosher foods, speak their own language, and not be cast in with strangers.

The Jewish people had already spread out over the entire East Side. Many lived as far north as Harlem. Far out in Brooklyn, a Jewish community sprang up in Brownsville, where inhabitants lived on farms with goats and fowl. Another community also developed in Williamsburg. Cemeteries were located in Brooklyn and Jamaica; when one person wanted to curse another, all he had to say was, "You should be carried to Brooklyn," or "Into the earth you should go!" No one dreamed in those days that in time one would go to Brooklyn through the earth, and be obliged to pay a nickel for doing so! . . .

The Brooklyn Bridge was already opened to traffic and tolls were exacted from pedestrians as well as from passengers. On the East Side, on Orchard, Ludlow and other streets, signs reading "No Jews" became a relic of the past. Henry Street, once an avenue of trees like East Broadway now was devoid of them.

There were no more green lawns. Beautiful Rutgers Street and Rutgers Place exchanged their palaces for tenements. Our brethren, the children of Israel, who were never permitted to enter the building trades, now became builders. Immigration brought about all these changes. Snowballs were no longer hurled at Jews in the ghetto, nor the derisive epithet, "Solomon Isaac." A Jew was safe on the Lower East Side except for the area bounded on the north by Madison Street. If he appeared below the boundary line, he subjected himself to such treatment as would result in giving him a good view of the interior of Gouverneur Hospital . . .

Prior to the completion of my studies at the medical school, a dispensary known as "Beth Israel" was organized on the Lower East Side, where there were no Jewish hospitals. Our people either had to go to Gouverneur Hospital or to Mt. Sinai Hospital on 66th Street, both non-kosher institutions. I contributed my share of effort in making this venture a success. The president, a veterinarian, Dr Jacob Serling, became friends with me. Upon graduation, I was appointed Attending Physician in the dispensary under the supervision of an elderly Russian physician. The dispensary was located at 97 Henry Street, a half-block from my office at 19 Pike Street, where I had moved after saving several dollars for equipment.

Bluestone next described the way in which a physician entering practice made a living. The provision of pre-paid medical care and the use of the capitation method were not unknown. Although this country is widely believed to have been a bastion of private practice fee-for-service medicine, it actually boasts a long tradition of alternative forms of physician reimbursement, dating back to the 18th century payment provisions for the care of merchant seamen. The Eastern European Jews brought with them a similar tradition.

The Jewish community on the Lower East Side demanded that the dispensary provide free medical examinations for destitute persons who were too ill to go to the dispensary for diagnosis and treatment. It was then decided to select two physicians to render such service at a per visit fee of 25 cents, to be paid for by the institution. Persons requiring medical attention at home had to procure a card from the dispensary; the physicians were paid every two weeks on the basis of the number of cards returned. I had the good fortune to be selected for this service. My co-worker was Dr Igelska, a woman. The income from this source covered my rent . . .

. . . I joined several orders which flourished at the time, and was elected lodge physician in more than one of them. This was a good move on my part because these orders became a source of friendships with many who recommended others. My practice increased from day to day. My office was furnished with necessary equipment. In addition, I was the proud possessor of a small bank account.

The contract between lodge and physician called for free consultation of members with the doctor at the latter's home during office hours; patients ill at home were to be visited by the physician after office hours. Remuneration was computed on the basis of three dollars per annum per married member and one dollar per single member. An additional fee was granted for surgical and obstetrical cases and also for examination of all new candidates. The income might have been small for a physician of years practice, but for a young doctor seeking contacts, it was considered very good. There were many respectable families that did not take advantage of this service. When they appreciated services rendered by the physician, they usually paid him a fee. When at some future time the lodge physician did not care to fill the position any longer because of the pressure of private practice, he retained a large percentage of members as his patients because they had confidence in him. As far as my practice was concerned, confinements and recommendations by friends paved the way for its expansion.

. . . Attention to patients in the dispensary and making home visits kept me busy all day. While it is true that the work was heavy, its usefulness to me personally was beyond question; I benefitted in experience and in the increase of acquaintances . . .

. . . One day upon arrival at the dispensary, I saw a memorandum from the Medical Board to the effect that a strike was in progress against the management and that no physician should make his appointed rounds. I was surprised. I knew that garment workers and other working men struck, but not doctors! Thinking that the ruling might possibly not apply to me because I was attending destitute patients in the home, I went to Dr Isaacs, a son of the former principal of the Talmud Torah, and asked his advice. I also inquired as to the cause of the strike and as to the moral right of refusing to attend to the sick when called upon to do so. He told me there would be a meeting that night and he would inform me the next day. The next morning he advised me that Dr Igelska and I were exempt from participation in the strike . . .

. . . When the Hebrew Free School became part of the Hebrew Institute, we bought the building in which it was housed, 206 East Broadway, and converted it into a hospital. Although we were able to purchase it at a low price, the down payment was raised only by assiduous work. I contributed effort and energy in the public relations campaign necessary to raise the funds for the institution . . .

The Board of Directors . . . at one of their meetings to which I was invited . . . passed a resolution of appreciation for my devotion to this.

At this same meeting, I was asked by the Board of Directors to recommend members for a new Medical Board. "I am willing to do this," I told them. "But with the provision that I be given *carte blanche* to choose whomever I wish. I also want the new Medical Board to have complete control over all medical affairs related to the hospital." Many members of the Board were opposed to granting me powers which seemed excessive to theirs. They insisted that the Directors confirm or reject all my appointments. As for permitting the Medical Board to control medical matters, this they consented to do. Notwithstanding their objections, I persisted in my refusal to subject any recommendations to a lay body.

I told them that when God created the world, He proceeded with his plans as all autocrats do. When He said, "Let there be light," the command was carried out forthwith. Every day He revelled in the thought that His orders were obeyed without question or delay. That which he himself created was perfect. On Friday, He called together His cabinet, the Ministering Angels, and said, "Let *us* make a man." He asked for advice on how to proceed. Well, what do you think? Shortly thereafter He cried out, "For it repenteth Me that I made them (Genesis VI:7). I regret having created such Paskudnyakis! [Note: 'Paskudnyak' is defined as a nasty and disagreeable person, brash, offensive.] Had He relied upon Himself and not upon His Board, He might have fashioned a perfect man for whom He would have felt no contrition! Everyone laughed; it was decided to give me *carte blanche*. On the next day I saw all the members of the old Medical Board and convinced them to return to service in the dispensary. I joined them as a member of the new Medical Board.

The Beth Israel Hospital grew by leaps and bounds, primarily because there was no true Jewish hospital on the East Side where a Jew, especially an immigrant Jew, might go, speak his own language and eat kosher food. Rich orthodox Jews, many of whom lived uptown, joined the Board of Directors. It did not take very long before it was decided to build a large hospital with all modern improvements. The Hospital and School for Nurses was constructed on the entire block from the corner of Jefferson and Monroe to the corner of Jefferson and Cherry.

When the new building was completed, word circulated among the Medical Board members that it was improper for me, as one of them, to receive any compensation for services in the homes of the destitute. Either I was to resign my membership on the Board, or give up accepting fees for visits. I agreed that their argument was valid. I consulted my wife, who advised that I re-

linquish fees and retain my membership on the Board. This meant cutting a huge slice from my income, which I still needed very badly. My wife said, "The future ought to be dearer to us than the present. We suffered so long, let us do so a little longer but grow with the hospital." Once again, I followed her advice.

The services at Beth Israel became departmentalized and I became one of the chief physicians on Internal Diseases. The duration of service was three months. My class in the dispensary was the largest and two assistants were assigned to me. The work in the hospital and dispensary as well as in private practice became heavier; my entire time was occupied and I had to curtail extra-professional activities.

In the hospital, as in the dispensary, my approach to patients was always a friendly one. Many patients remained my own and they recommended others. They liked me because I did not play the role of a professor who charges high fees. My fees were based upon ability to pay; the poor were exempt . . . In addition to devoting three days a week to the hospital and dispensary, I had to attend a clinic on Internal Disease at the college dispensary. My chief was Professor Alfred Loomis, who was considered an authority on his field in America, and whose text book was standard for many colleges. [Note: Dr Alfred Lee Loomis, 1831-1895, a specialist in diseases of the heart, lungs, and kidneys, was a proponent of the use of the Adirondacks for treatment of tuberculosis.] Once a week I had to prepare interesting cases for presentation by him to the college students . . .

LIFE IS WITH PATIENTS

Bluestone relished human interest stories of the patients he saw in their tenement walk-ups, particularly surgical and confinement cases. He took as much pleasure in those of his colleagues, putting them in his own memoirs. A favorite among them came from Dr Abraham Jacobi. Jacobi, for whom the hospital in the Bronx was named, was considered the foremost pediatrician of his day. He was a consultant at the Beth Israel Hospital.

. . . I once had occasion to call Professor Abraham Jacobi to examine a ward patient of mine at the hospital. He promised to visit on the following day. When he completed his examination, he asked to see my other patients. After he made his rounds, he expressed satisfaction with my diagnoses and treatment of the cases. We sat in the office together while he related anecdotes of his early life soon after arrival in the United States in 1848. [Note: Dr Bluestone was mistaken; Dr Jacobi did not leave Europe until 1853.] One of these is worthy of record.

When Dr Jacobi was a very young man, he escaped Germany during the revolution. Naturally not having any capital, he opened an office in a basement located at Canal and Chrystie Streets. His fee was 50 cents a visit, when such rare occurrences took place. His leisure time was spent in a drugstore on the corner of Division and Clinton Streets, where occasionally he received patients at 25 cents per visit. It does not require any stretch of the imagination to know how large his income was. "Once," he related, "when I left the office to go to the drugstore, I was accosted by a heavy set German, a fellow townsman of mine, an 'alright-nick' [according to Howe⁷ this term referred to an immigrant who had become wealthy], who warmly greeted me, 'Oh Abraham! How goes it?' 'Very fine,' I answered him cordially. 'You are a doctor,' he continued, 'You can give some advice. Last night I attended a banquet and I feel rather seedy. I must go to business, and I don't know what to do to clear myself up.' That dear compatriot of mine, I thought to myself, who has enough money to spend on champagne doesn't care to spend a 25 cent piece for advice—must I give him advice free? So I said to him, 'Please show me your tongue!' and he stuck out his tongue. 'Please close your eyes' and he closed his eyes. I left him standing just that way. If perchance you ever pass Canal and Chrystie Streets, you may see a German standing with his eyes shut and his tongue out. He's probably waiting for me to tell him to open

his eyes. He must be old by now; this occurred more than fifty years ago!"

The encounters with patients of his own that Bluestone remembered and chose to record in his old age are highly revelatory, not only of the traumatic impressions they left upon him as a practitioner, but of unchanging human nature, and the way poverty medicine of the day was generally practiced. Most of his patients, in fact, would be immediately recognizable to the physicians of today who continue to treat the hypochondriacs, the worried well, the entitled, the worshipful, and a whole host of those seemingly upright citizens whose illnesses call forth major regressions in civilized behavior of a decidedly sociopathic nature.

. . . A lodge member once called me in the evening and asked that I come to Columbia Street near Houston, quite a distance from my office. When I reached the house I saw several women chatting in front of the building. I inquired as to the number of the apartment of the family I was seeking and a heavy set, healthy-looking woman indicated that she, herself, was the one who called. She then escorted me to her fifth floor apartment. I panted heavily after climbing those steep flights of stairs! We entered the apartment and I asked for the sick one. "I am the sick one," answered the same woman, "I have pains in my throat. Examine me and let me know what the trouble is." "You will be good enough," I said to her, "to come to my office tomorrow morning between nine and eleven and I will examine you then. I am not obligated to attend you at home." I took my hat and medicine bag. "Well," said the patient, "You are here already. Examine me and I will pay you because I can't walk such a distance to your office." "Yes," I remarked, "You can't walk such a distance, but the doctor can, eh? I won't examine you even if you really want to pay me." I then left.

The next morning the woman's husband came to my office and said, "Doctor, yesterday you did not want to examine my wife. Perhaps from your point of view you were right. Today her condition became worse and she is in bed. Will you be kind enough to visit her?" "Well," I had no choice but to reply, "If she is in bed, it is my duty to go." Immediately after office hours, I went to the home. When I reached the third floor, I looked up and thought I saw the patient going to her room upstairs. I ran to the fifth floor, knocked and entered in time to see her lie down in bed, fully clothed. There she lay moaning, complaining of pains in her entire body. I understood what motivated her action, so I advised that she disrobe and submit to a complete examination. She complied and I examined her thoroughly, saying that she had no realization of how seriously ill she was; her heart beat was abnormal; she was to remain in bed at least two weeks and be visited regularly; she was to be extremely careful and not move from side to side lest her heart cease beating, God forbid, and then everything would be over. Possibly it would be best if she were to be hospitalized, or a day and night nurse engaged to care for her at home? After giving my suggestions for treatment, I left.

The next day I visited my patient and found her seated at the table with her family eating cholent. "What's this?" I looked surprised. "You risked leaving your bed?" "Doctor," she smiled in response. "We understand each other. I wanted to play a joke on you, so you repaid me measure for measure. Here are two dollars for your trouble and let us remain friends." From then on, she always paid me for any services rendered.

Patient misconceptions about the attributes of a competent doctor were as prevalent then as now. Bluestone notes the following:

. . . I heard from a friend whose rich daughter refused to call a young doctor for her sick child; she insisted on an older gentile

doctor whose fees were higher. This older physician diagnosed the case as one of diphtheria and made three home visits daily. During the second week, he made two visits daily. The child improved, was playful, had no fever, and generally appeared much better and more spirited. The child's grandfather asked that my advice be sought. I made a thorough examination, found no indication of any illness and told the parents that the child probably was ill, but not at the time of my visit. To me, the child appeared normal. "Nevertheless," the mother said, "Step in several times and keep an eye on the child. Do not spare my money." "It is not necessary, my dear lady," I tried to assure her, "Your child is healthy. I won't take your money needlessly."

A fortnight later my friend met me. "Forgive me," he said, "but are you a business man! With such tactics you will never make a success. As soon as you told my daughter that you didn't find it necessary to come any more, she called the other physician and told him that another doctor and pronounced the child cured." "All right," he answered, "Go to the other man! I don't care to assume further responsibility for the child's life." "She had a difficult time convincing him to continue his visits. Now she believes the other doctor saved the child from a sure death. We know that the child was not sick, but my daughter has plenty of money. Had you listened to her that time you would have had not only the money but the credit also." "Well," I responded, "I hope during my entire life to be a good physician and a poor businessman. Every dollar I earn must be earned honestly and without swindle or deception."

... Once while returning home from a confinement case late at night, I visited the store of my neighbor, the druggist, in order to take stimulant before going to bed. Being very tired, I dozed a bit. I heard a woman cry and beg for something, and a man answer her. Waking up, I saw Dr. G, a leader among the East Side socialists, arguing with a poor woman. She was looking for a physician who would take care of her only child, who had developed a fever. She did not have the \$3 fee that Dr. G wanted, being a widowed scrubwoman who could not afford to pay more than a dollar. The doctor argued that his usual fee for night visits was \$5, but he reduced it to \$3 for her, adding that if she could not afford that, she might go to a police station where a doctor would be gotten for her gratis. The woman wailed bitterly and pleaded with him but her plea fell on deaf ears. I remembered that when Dr. G was a student, I was his family physician, and received no fees for my services. I then arose and said to the woman, "Come, I will go with you to see your child without any fee." She looked at the druggist, who assured her that I was a competent physician. Both of us climbed the four flights to her home where the child lay very ill. I made five visits without fee. It was worth it to me to give that Socialist a lesson.

A similar incident occurred two years later, while I was walking home at midnight from a confinement case. I entered a drug store to purchase a refreshing drink. Upon leaving, I was accosted by a bum, who, seeing my medicine bag, asked if I were a doctor. His child was sick and he could not wait until morning; he begged me to go to his home on Madison Street. Noting his appearance, I was actually frightened, and afraid to go with him. I had heard of many robberies practiced on unsuspecting physicians. There were quite a few dollars in my pocket and I was unwilling to risk a visit with a man dressed like an underworld character. I tried to avoid going with him, but he pleaded that he was unemployed and penniless. He promised to pay the necessary fees immediately after reemployment. This made it incumbent upon me to go with him and risk the trip.

When I reached the man's home, I was surprised to see a Mizrach on the wall. [Note: The Mizrach indicates the Eastern wall of a dwelling, orienting it towards Jerusalem.] "Are you Jewish?" I queried. "Yes," he answered, "My wife is native born, and I come from Poland." I attended his child and promised to call daily. The child had diphtheria. At first I made two visits daily, then afterward one, until the child was cured. Long after this incident, a man came to my office and asked how much he owed me for my services. I did not recognize him, for he was shaved and appeared happy. He disclosed his identity and said he

had come to pay me his debt. I explained that I had considered his a charity case, but he refused to recognize it as such. He had procured a good job, and therefore brought me \$10. I said to him, "Better pay your grocer and butcher! If you insist upon paying me, bring a dollar every week to my office." "No," he answered, "Your debt takes precedence. I shall never forget your attention to my child." He placed the money on the desk and left. He remained my patient ever since.

I recall a charity case in which a child had pneumonia. I visited twice daily. The family appeared destitute, but I learned that another physician was called without my knowledge and was paid a fee of \$5. Naturally I ceased my attention to the patient.

Bluestone's patience was not inexhaustible nor his humor unfailling.

... The incidents related remind me of King Solomon's proverb. "Cast your bread upon the waters, for you shall find it in latter days." These proverbs have exceptions also. There are more swindlers than honest people.

Dr. Francis Huber, a prominent physician and lecturer at Columbia College of Physicians and Surgeons, once recommended a confinement case to me. It appears that a midwife advised the calling of a physician because the case was a difficult one. The husband had consulted Dr. Huber regarding his wife, and Dr. Huber in turn, sent the man to me. Huber's case, I thought, surely would pay well. I went to the home and found dire poverty. Not one piece of furniture was of any use. In fact, there were only a broken table and torn sofa testifying to the destitution. I examined the woman and decided that it was necessary to use instruments. The case was serious and another physician had to be called to administer chloroform. The man began wailing, "Where will I obtain the money with which to pay the other doctor?" He asked me to try delivery without chloroform. What could I do? I did so and was successful.

When the time came to pay, he asked my fee and I said, "My usual fee is \$25 for such a case, but I see you are poor. I will cut it in half." All he could afford was \$5. "God Almighty will send you a rich patient in recompense," he said. I took the \$5 on the premise that it was better than no fee at all.

A few days later, Dr. Huber, who had been away for the weekend, met me and inquired after the welfare of the patient. I told him how difficult the case had been, the need for chloroform, and the man's plea that he could not afford to pay another physician. "And what did you receive?" he asked, I would have felt humiliated had I told him the truth, so I answered, "\$15." "The faker," Dr. Huber said, "I told him your fee would be low, \$25. He risked the life of his wife by not calling another physician at your request." "But, Dr Huber," I added, "had you seen the poverty-stricken home, you would talk differently!" "He's an old patient of mine," he asserted. "He pays me \$5 a visit. He owns two tenement houses and has a big income. In spite of this, he lives like a pig."

On a certain Friday night, when it was frightfully cold and stormy, a man awakened me and told me his wife was in labor and the midwife advised calling a physician. I accompanied him to his home on far away Ridge Street. It proved to be another instrument case. I asked the midwife if the man was able to pay. She answered that the man was not rich. When I had finished and was ready to leave, I saw the man made no sign of offering to pay me. I then said to him, "Mister, I have finished; you will please be good enough to pay me." "Immediately after the Sabbath," he answered, "I will bring a dollar to you." "The fee is \$10, not \$1." I insisted. He was obstinate about it and repeated, "I told you, I will bring the \$1 to you after the Sabbath." "The fee, Mister," I reiterated, "is \$10 payable now; I don't care to trust you." He swore by his wife and his children, his beard and forelocks, that he had not a cent in the house at the moment. He promised to pawn some personal belongings after the Sabbath and bring a dollar to me. To argue with him further was futile, so I said, "All I can do for you is this; if you want to pay now, I'll

accept \$5, but if I must run after you to collect the money, the fee becomes \$10." He kept insisting, however, that he had no money in the house.

I became impatient and warned him, saying, "I do not want any fee, but I am going directly to the police station to tell the authorities that a man pulled me out of bed in such stormy weather and refused to pay me for my services. Meanwhile, you can spend the night in jail." When I made a motion to leave, he cried out, "Wait a while. I'll ask my wife if she has any money." He entered the bedroom and then emerged with a \$10 bill, which he tendered with a request that I give him change. "In reality," I said, "You are not entitled to change. A Jew who swears falsely does not deserve sympathy. Nevertheless, in order to demonstrate the sanctity of a person's word without a vow, here is \$5." I then left the home.

THE FABRICATING PHARMACIST

Bluestone records not only the vicissitudes of hospital management and patient care but the realities of dealing with fellow health professionals as well. Quality control, now all too well bureaucratized, was very much the concern of the individual practitioner. Consider, for example, the case of the "fabricating pharmacist," who remained Bluestone's nemesis until he was finally vanquished, along with his bottles of useless colored-water potions:

In accordance with custom, in those days druggists maintained a close relationship with physicians, the former referring patients and the latter referring prescriptions. The druggist on the corner of Henry and Pike Streets approached me regarding such a reciprocal relationship. I soon discovered that he was a fabricator; he would manufacture "cases" in order to receive my trade. On one occasion, he asked me to see a patient with him. While walking to the home, he told me that a man had entered his drug store, asked for castor and said that his child had fever. "I didn't sell him castor oil," continued the druggist, "but went with him to see the child. I scared him a little by leading him to the belief that the child had diphtheria. I told him a physician must be called at once. You should know, therefore, doctor, that this is a case of diphtheria. You will visit the patient several times and I will have more prescriptions. The child will recover rapidly; you will be the good physician and I the good pharmacist." I entered the home with him. The child's temperature was normal and throat negative. I prescribed a laxative and reassured the worried family. The druggist censured me severely saying, "You aren't a business man and will never build up a practice." I answered that "If ever I find it necessary to build a practice through fraud and deceit, and to take from the destitute money that does not belong to me, which in reality is robbery, I'd rather be a bricklayer than a physician!"

... I became more and more skeptical of the honesty of my druggist and of the method he used in compounding prescriptions, but as long as I did not have proof, I continued my relations with him. A patient once came to me with a terrible headache. After examination, I prescribed powders with instructions that he take one, and if he experienced no relief within an hour, that he repeat the dose, for a second powder surely would produce the desired result. A few hours later, my patient returned with the same complaint, although he used up all the powders. Suspecting that he had not received the correct medicine, I gave him an exact duplicate of the prescription with instructions to have it compounded at another pharmacy and report back later. Shortly thereafter, he returned to thank me; he had received the desired relief after taking one powder.

I went over to my druggist and found him absent from his store for the moment. I asked his clerk to give me a powder such as I had prescribed for the other man that morning, because I, too, had a terrible headache. He searched the store but in vain. I entered his laboratory in the hope that I would possibly find evidence to confirm my suspicions. Suddenly I heard the voice of the

pharmacist, asking whether any sales had been made in his absence. "Yes," answered the clerk, "25 cents quinine. I did not find enough to give the customer." "A fine businessman you are," thundered the druggist, "Why didn't you substitute Epsom Salts, which are also bitter? The customer would have thought it was quinine and I would have retained him as a customer." At this point I walked out of the laboratory very much to the confusion of the druggist. I apologized for the intrusion but from then on, I warned my patients to beware of him.

Eventually the pharmacist discerned that he was losing business because of me, so he joined hands with another physician who practiced across the street from my home. He and the doctor would pass spitefully by my window, in order that I might see how much I had harmed myself by not patronizing that druggist.

Once he came to me and renewed a bid for friendship, offering to send two patients for every prescription I referred to him. I told him my reputation was worth more in my estimation than the few dollars I would receive through his interest. I added, "You hold on to Dr. S and I will retain my relations with a druggist who will dispense exactly what I prescribe." On the next morning, a woman called me for professional care. She had confidence in my neighbor, that druggist. I could not wean her away from him, nor could he alienate her from me. I examined her, prescribed appropriate medicine, and left to see other patients. Upon my return to my office, I found the druggist and two women waiting for me. He said, "You see, I keep my promises. I received a prescription of yours from Mrs. B, so I brought you two patients." I thanked him cordially and asked the women who had recommended them to me. They pointed to the druggist. I said, "I regret that I do not treat patients introduced to me by a druggist; they must come on the recommendation of others." The three of them departed.

A short time later, a man called and explained that he had bought the drugstore on the corner and had been deceived as to its worth. He found all bottles filled with colored water. There were no signs of useful drugs; new stock had to be bought. He sought my friendship and I promised that if he dispensed according to specifications, he could count on my patronage. We remained very friendly from then on.

THERE IS A LIFE BESIDES MEDICINE

As the century drew to a close, the competition for Bluestone's time grew more intense. In 1897, preparations were begun for the First Zionist Congress to be held in Munich, Germany, the following year. Because of the protests of the German Rabbinate, the Congress was convened instead in Basle, Switzerland. It was to become the historic convocation that initiated the political Zionist movement's establishment of a Jewish state half a century later. Bluestone was asked to become a delegate, but "... it was impossible for me to leave town for several weeks; such an absence would have ruined my practice. Besides, my service at the hospital during July, August and September would have been disrupted. I was heart-broken not to be able to attend so momentous an historical occasion, but I was compelled to deny myself that satisfaction ..."

Five years later, however, Bluestone succumbed to the temptation to attend a subsequent Congress.

... One can imagine how difficult it was for me to leave my office for two months, a luxury for a doctor with a practice. My friends strongly urged that I go and I had to yield ... I arranged with the Medical Board concerning my services at the Beth Israel Hospital. It was my turn to be in charge of the wards. Inasmuch as other physicians did not wish to disturb their vacation schedule, I offered to resign from hospital service if my application for a European vacation were denied. After considerable argument, it was decided to arrange for a substitute during my absence. I engaged another physician to care for my practice during my leave. He was to receive board and lodging free; I was to receive



FIGURE 2. Portrait of Joseph Isaac Bluestone, MD, late 1920s. The Hebrew inscription, a rhyming couplet, translates: "This is the shadow (photograph) of my life, here I am, even though I go, and am no more."

fees from confinements and deferred payments. Cash fees were to belong to him. I gave him a large list of confinements, at the same time requesting that he treat everyone courteously. I specifically asked that he waive fees for the indigent, just as I did. He promised faithfully to comply with all my wishes

When Bluestone returned, however, on the 19th of September, 1903, he found his office a shambles, all promises broken, and like many other physicians before him, vowed never again to hire a locum tenens.

Bluestone never clearly stated the reasons for his growing disenchantment with the Beth Israel Hospital. As mentioned, his competing interests may have begun to take precedence. His dependence on the hospital for financial security may no longer have been as prominent. Perhaps he felt that an established institution no longer needed him, and it was time to turn his talents to other developmental areas. In any event, there is no doubt that he believed that the leadership of the hospital had strayed from its mission. The most prominent Yiddish language newspaper of the day, the *Forward*, documented the bitter acrimony, the charges and counter charges concerning dereliction in the hospital management.⁸ As Bluestone wrote, in a series of articles that supported Bluestone's experiences . . .

The Beth Israel Hospital engaged a young Hungarian as Superintendent. He pursued a carefree life with the head nurse, a good-looking gentile German woman. Both neglected the hospital terribly. At that time, I was Chairman of the House Commit-

tee. The doctors frequently complained to me that nurses were not available upon call, and that necessities were not supplied upon request. The Medical Board sharply protested this laxity. Apparently the president's family physician, an influential power in the insitution, opposed any change in management; hence the Superintendent continued to do as he pleased.

One day a house physician called me up and asked that I come to the hospital immediately for consultation. A man had been brought in suffering from a stroke. When I called to see the patient, I noted the absence of an icebag on the patient's forehead. When asked the cause for this, the intern told me that "the head nurse doesn't want to supply any more ice bags." I immediately conferred with the superintendent and sharply protested such negligence and lack of attention. He promised to have an icebag brought to the patient. When I paid my second visit and saw the icebag, I asked the intern if he had received it the same day. He declared that he had received nothing from the office, but another patient had died; he had removed an icebag from the body and used it

The final blow came apparently when Bluestone saw that his hopes for a hospital that would serve his Eastern European community without the snobbery or prejudice of the uptown, more assimilated Jews were doomed.

. . . There was a prominent Lithuanian Rabbi confined to a ward under my care. I asked Dr. Isaac Adler, the consultant, to examine him and render an opinion. He told me he believed "All Orthodox rabbis are syphilitics and ought not be admitted to a private hospital." I became terribly perturbed over this, and on December 6, 1906, immediately after the incidents mentioned, I submitted my resignation as Visiting Physician after 16 years of service. Professors Einhorn, Guire, Huber, Halpern, Gordon and Romm resigned with me. I was appointed Emeritus Visiting Physician with certain privileges. However, after I submitted my resignation, I ceased all connection with the Hospital.

No further mention is made of the Beth Israel Hospital in Bluestone's memoirs. He continued his communal activity, became a prosperous physician, raised his large family in the comfort and security of two adjoining brownstone houses, and travelled widely. Like his counterparts of today, he even dabbled unsuccessfully in real estate, owning (and prematurely selling) all the land around what is now the Dyckman Street subway. He died in 1934, several years after a stroke gave him the enforced rest and leisure necessary to record his memories of his life and the turbulent times in which he was privileged to live.

Acknowledgment. The memoirs and scrapbooks of Dr Joseph Isaac Bluestone are found in the archives of the American Jewish Historical Society in Waltham, Mass, to which I am indebted for the use of this material.

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Tuberculosis of the hand and wrist

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In 1895, Osler¹ attested to the ubiquity of tuberculosis in his *Principles and Practice of Medicine*, when he quoted a saying of the time that, "every man has, in the end, a little bit of tuberculosis." Since the end of World War II, the fall in the incidence of tuberculosis has been dramatic. This decline is due to improvements in living conditions, the discovery of effective antimicrobial agents, and the elimination of infected milking herds. With the advent of acquired immunodeficiency syndrome (AIDS), with immigration from areas of endemic disease, and with persistent substandard living environments, this trend has been reversing in some areas of the US. Tuberculosis remains a major public health problem in the United States.

Historically, tuberculosis of the hand and wrist accounts for less than 1% of extrapulmonary tuberculosis. We report two cases of tuberculous infections of the hand and wrist treated with surgery and antituberculous medication.

CASE REPORTS

Case 1. An apparently healthy 35-year-old, non-Haitian black man presented with a four-month history of progressive painless fusiform swelling of his right distal middle finger. He had experienced no recent trauma or known exposure to tuberculosis or other mycobacteria. He denied heavy alcohol use and denied intravenous drug use. Examination showed a nonerythematous, non-tender fusiform swelling of the middle finger at the distal interphalangeal (DIP) joint level with no discrete borders (Fig 1). The area did not transilluminate. The remainder of the physical and hand examination was normal.

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FIGURE 1. Fusiform swelling of the long finger (case 1).

Radiographs showed periosteal reaction and narrowing at the DIP joint (Fig 2). An intermediate strength purified protein derivative (PPD) skin test was positive. Chest radiographs, sputum smears, and cultures were all negative. Testing for human immunodeficiency virus (HIV) was also negative.

Exploration through a volar incision showed a poorly demarcated fatty tumor in the subcutaneous tissue and distal tendon sheath extending into the joint. On the dorsum there was extensive involvement subcutaneously and around the distal extensor tendon. The visible tumor was debulked by excision and curettage. Histologic evaluation showed necrotizing granulomas and gi-



FIGURE 2. Radiograph showing soft tissue swelling, distal joint narrowing, and periosteal reaction (case 1).

ant cells consistent with tuberculosis (Fig 3). An acid-fast smear was negative, but cultures were positive for *Mycobacterium tuberculosis*. Viral, fungal, and routine bacterial cultures were negative.

After surgery, the patient was started on a regimen of oral isoniazid, 300 mg qd, oral rifampin, 300 mg twice a day, and oral ethambutol, 1 g qd (15 mg/kg/qd). Though the wound healed per primum and there was progressively less swelling, serial radiographs showed progressive joint destruction, and by the fifth month the joint showed excessive motion of lateral stress. Despite this, the patient continued his employment as a maintenance worker without disability. At the end of the seventh month of therapy, there was no clinical or radiographic evidence of disease progression. The drugs were then discontinued due to poor patient compliance. Nine months after his initial presentation, the patient is off medications and free of symptoms. Based on clinical and radiographic evaluations, the DIP joint is spontaneously fused at 20 degrees of flexion. There is no evidence of other areas of tuberculous involvement.

Case 2. A 26-year-old white man with rheumatoid arthritis involving multiple joints presented with acute right wrist swelling. Occasional prior episodes had been attributed to his arthritis and were treated with gold and physical therapy. At this time he was on maintenance therapy with penicillamine, aspirin, and prednisone. There was no history of fever or chills. He had no known exposure to tuberculosis, and he was not at risk for occupational exposure to atypical mycobacterium. He denied heavy alcohol use and intravenous drug use. He re-

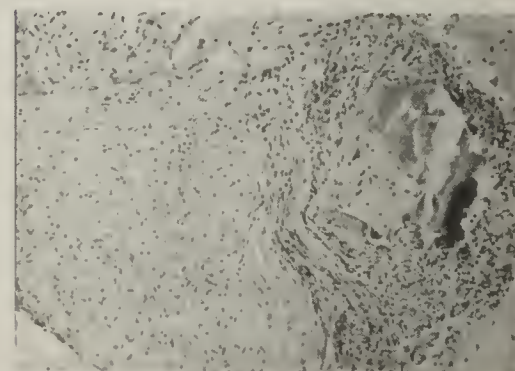


FIGURE 3. Granuloma encroaching on dead bone (case 1) (hematoxylin-eosin stain; original magnification X 250).

ported blunt trauma to his wrist approximately six years before. Examination at this time showed a tender, warm right wrist with painful flexion/extension from 5 to 45 degrees. Neurovascular examination was normal, and tendon function was intact. The rest of the hand and physical examination was normal. Radiographs showed extensive destruction of the right wrist (Fig 4). A white blood cell count and sedimentation rate were normal.

Wrist joint aspiration produced milky fluid with a negative Gram's stain and culture. Dorsal wrist exploration showed hypertrophic joint and tendon synovium, which was excised, and bony changes grossly consistent with rheumatoid arthritis. Acid-fast staining of the synovium was negative, but necrotizing granulomas were found on histologic analysis. Intermediate strength PPD and cultures were both positive for tuberculosis. Chest radiographs, sputum smears, and cultures were all negative.

The patient received oral isoniazid, 300 mg qd, and oral rifampin, 300 mg twice a day for nine months. Evaluation at nine months showed no clinical or radiographic evidence of disease progression. In spite of this, wrist arthrodesis with iliac bone graft was required because of painful, limited function. This procedure produced a solid fusion, giving the patient relief from pain, 70% of his normal pronation/supination, and good grip strength (R-100, L-120 pounds). Five years later, he remains free of symptoms with no antituberculous medication. There is no evidence of other areas of tuberculous involvement.

DISCUSSION

Tuberculosis remains a major health problem in the United States. From 1963 to 1985, the incidence of tuberculosis in the United States declined an average of 5.9% annually. In 1986, 22,768 cases were reported to the Centers for Disease Control, representing a 2.6% increase in the number of reported cases.² This increase is attributable to a high incidence of tuberculosis among HIV infected patients, increasing immigration from areas endemic for tuberculosis, and persistence of high risk among city blacks, Native Americans, and the homeless. Of note is the increasing incidence of extrapulmonary presentation among both AIDS and non-AIDS populations. Also of concern is the higher number of resistant strains among patients from other countries.³⁻⁶

Extrapulmonary tuberculosis can involve various sites including the central nervous system, pericardium, genitourinary tract, gastrointestinal tract, and others. It can result from lymphohematogenous spread; dissemination of contaminated pulmonary secretions to the upper airway, mouth, and gastrointestinal tract; or direct extension to contiguous tissue.⁷ Sites seeded by lymphohematogenous spread may remain dormant for some time, then appear

without evidence of recent or remote pulmonary tuberculosis.

Of the various sites, musculoskeletal tuberculosis accounts for less than 5% and usually involves the spine, hip, or knee. It seems to progress from tenosynovium to bone, though it can present with either bony/joint involvement or synovitis, or a combination of the two. Lefond,⁸ in 1953, reported 230 cases of adult skeletal tuberculosis, only six of which were limited to the hand and wrist. Hodgson and Smith,⁹ in 1972, reported only 14 cases of tuberculosis of the wrist out of more than 2,000 cases of osteoarticular tuberculosis. Benkedache and Gottesman¹⁰ reported 388 cases of skeletal tuberculosis in Algeria from 1971 to 1980. Only 6.9% of these cases involved the hand or wrist, and only two of these involved the DIP joint, as in the first patient described here. The Geisinger clinic,¹¹ in 1986, reported only five cases of wrist tuberculosis over a 15-year period, and no cases involving the hand.

One of the characteristic features of extrapulmonary tuberculosis is delay in diagnosis due to either late patient presentation and/or misdiagnosis. Walker¹² reported on nine cases with a 19-month average delay from onset to diagnosis. Benkedache and Gottesman¹⁰ reported on 27 cases in which there was a 17.5-month average delay. Tuberculous synovitis of the hand/wrist mimics several other diseases, including: rheumatoid arthritis, rheumatoid synovitis, sarcoidosis, and nonspecific synovitis. Mayers¹³ reported on tuberculosis presenting with carpal tunnel syndrome. Bush and Schneider¹⁴ reported on four patients who had repeated aspirations of what were thought to be ganglia before the diagnosis of tuberculosis was made. Ekerot and Eiken¹⁵ reported cases that were unsuspected even at surgery. Where there is bony involvement as well, the differential diagnosis will vary with the stage of presentation. It may include benign bone tumors such as enchondroma or osteoid osteoma, pigmented villonodular synovitis, pyogenic infection, rheumatoid arthritis, hyperparathyroidism, and brucellosis.¹⁶

While a history of tuberculous exposure is often negative, as in these two patients, various risk factors for osteoarticular tuberculosis may exist. These include alcoholism, diabetes, chronic debilitating states, corticosteroid injection, and antecedent local trauma, as in the second case.¹⁷ Symptoms of tuberculosis of the hand and



FIGURE 4. Radiographs showing extensive destruction of the right wrist (case 2). Left, anteroposterior view; Right, lateral view.

wrist include swelling, fistula, inflammatory reaction, and functional impairment. Although tuberculosis affects both bone and synovial membrane, synovitis is usually the early symptom. The synovitis and swelling appears gradually, and the patient cannot recall a particular time of onset. At a later stage, the overlying skin may become reddened, ulcerated, and secondarily infected, a condition known as spina ventosa.

Sedimentation rate and white blood cell count are typically normal. PPD tuberculin skin tests are usually positive, but a negative result, especially in the elderly or patients with AIDS, does not exclude the diagnosis.¹¹ Pain is common with bony involvement, while tenosynovitis is usually painless. Radiographs may show joint narrowing, periosteal reaction, and periarticular osteopenia progressing to cystic lesions with or without sequestra. Unfortunately, as with the clinical symptoms, the radiographic changes may be delayed and insidious. Unlike pyogenic infection of bone, which may show evidence of bony destruction within hours or days, the tubercle bacillus may not provoke an immediate osteogenic reaction. Testing for concurrent active tuberculosis via physical examination, sputum analysis, and radiographic evaluation is commonly negative. While Evanchik et al¹¹ reported a 45% incidence of concurrent pulmonary tuberculosis based on radiographs or sputum, other series report lower figures.^{12,18}

The key to early diagnosis is suspicion and subsequent biopsy. Unless appropriate cultures and sections are performed at surgery, the diagnosis will not be apparent. Presumptive diagnosis is made by the presence of acid-fast bacilli on direct examination of synovial fluid or tissue, and/or the presence of characteristic caseating granuloma with giant cells. These may not, however, be present in each case and are not diagnostic on their own. Subsequent culture of the acid-fast tubercles from either fluid or tissue confirms the diagnosis.

As soon as a provisional diagnosis is made on the basis of histology and clinical features, drug therapy should be instituted. If cultures prove positive, then therapy is continued; cultures may take more than six weeks to grow. Medical therapy consists of between six and 12 months of isoniazid, in various combinations with ethambutol, rifampin, streptomycin, or pyrazinamide. Recent studies with pulmonary tuberculosis

have shown promise for abbreviated treatment schedules, with improved patient compliance.^{19,20} Sputum conversion was achieved without a significantly higher rate of relapse or adverse reaction. The higher rates of compliance are significant, as noncompliance predisposes to treatment failure and to subsequent development of resistant organisms.

In contrast to pulmonary involvement, tuberculosis of the hand and wrist is more readily accessible to surgical intervention. Adjunctive debridement may hasten recovery by removing diseased, poorly functioning tissue. This should add to the efficacy of drug therapy. Though antituberculous drugs will provide cure, the ultimate degree of function is largely dependent on the time of presentation and the degree of joint involvement.^{21,22} With gross bony involvement, as in case 2, primary arthrodesis should be considered. If a trial of less aggressive management is chosen, there should be close clinical and radiographic monitoring for disease progression, such as persistent inflammation and sinus formation. Bush and Schneider¹⁴ reported on two cases with wrist involvement in which synovectomy alone proved to be inadequate. One patient ultimately had a draining sinus which was attributed to inadequate bony debridement and possibly failure to perform a primary arthrodesis. In their study, Benkedache and Gottesman¹⁰ eventually fused two of eight involved wrists, though they limited their initial surgery to biopsy rather than a more extensive therapeutic debridement. With cases of dactylitis, adequate control and function can often be achieved without arthrodesis or amputation, as in the first patient presented here.⁷

Other mycobacteria of note that affect the hand are *M marinum*, *M kansasii*, *M intracellulare*, and *M avium*, the so-called atypical mycobacteria. These organisms are distinguishable from tubercle bacilli by a high degree of isoniazid resistance, by differing abilities to produce catalase and niacin, and by their clinical presentations. The atypical mycobacteria may be distinguished among themselves by varying pigment production, growth rates, and clinical presentations.²³

Mycobacterium marinum is the most common mycobacterium to infect the hand, causing both superficial and deep infections. It does not cause pulmonary infection. Superficial cutaneous infection can be of the verrucous or more

common granulomatous types. Deeper infection is less common and typically involves the synovium of the flexor sheath of the finger or wrist, or extensor tenosynovium. *Mycobacterium marinum* is the most common in those who work in marine environments or with swimming pools or fish tanks.²⁴ Treatment is with antituberculous medications and/or surgery, depending on the degree of infection. Antibiotics of the tetracycline class have also shown great effectiveness.²⁵ *Mycobacterium kansasii* is best known for pulmonary disease that is almost identical to tuberculosis. It rarely causes infection in the hand and is fairly responsive to anti-tuberculous medication. *Mycobacterium avium* and *M intracellulare* are closely related and have received increasing attention with the advent of AIDS. Both rarely cause infections in the hand.²⁶

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Granular cell myoblastoma in an HIV positive patient

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Several neoplasms have been reported in patients with the acquired immunodeficiency syndrome (AIDS).¹ Granular cell myoblastoma, a benign Schwann cell tumor which shows a predilection for the upper airways,² has been reported in association with a number of disease processes associated with altered cellular immunity, such as lung carcinoma^{3,4} and sarcoidosis.⁵ We report here a case of granular cell myoblastoma that occurred in association with human immunodeficiency virus (HIV) infection.

CASE REPORT

A 52-year-old woman with a history of multiple admissions for bronchial asthma was admitted to the hospital with dyspnea and fever. Her medical history was also significant for chronic persistent hepatitis, as well as substantial abuse of cigarettes, alcohol, and intravenous drugs. Her family history was unremarkable.

On physical examination, the patient appeared to be a well-developed female in no acute respiratory distress. Her temperature was 100.5°F. Auscultation of the lungs revealed bilateral wheezing and scattered rales. Her heart sounds were regular and there were no murmurs or extra sounds.

Laboratory data were significant for elevated alkaline phosphatase (508 IU/L) and serum glutamic oxaloacetic transaminase (104 IU/L). The chest roentgenogram showed bilateral hilar adenopathy and a left upper lobe infiltrate, as did the computed tomographic (CT) scan of the chest (Fig 1). Sarcoidosis and tuberculosis were considered, and fiberoptic bronchoscopy was performed. White plaque-like endobronchial lesions were noted on the anterior aspects of both mainstem bronchi, as well as the orifices of the upper lobes (Fig 1). Biopsies of these lesions revealed histologic findings



FIGURE 1. Computerized tomography of the chest showing small endobronchial lesions (arrows) in both mainstem bronchi.

compatible with granular cell myoblastoma (Fig 2). Simultaneous biopsies of lung parenchyma showed no histologic evidence for sarcoid, tuberculosis, pneumocystis, or bacterial pneumonia. Pulmonary function tests at that time showed a moderate obstructive ventilatory defect with a reversible component, and no suggestion of upper airway obstruction on the flow volume loop.

As no source for her febrile illness was found, the patient was treated for legionellosis, on the basis of a positive *Legionella* serology; clinical improvement and defervescence were seen. She was discharged after a one-month hospital stay. About three

months later, generalized lymphadenopathy developed, and HIV testing was performed because of the patient's history of intravenous drug abuse. The ELISA and Western-blot were reactive for antibody to HIV-I, and a concurrent lymph node biopsy showed follicular hyperplasia consistent with HIV infection.

DISCUSSION

AIDS has a known association with Kaposi's sarcoma, various lymphomas, and squamous cell carcinoma of the buccal mucosa.¹ Metastatic small cell carcinoma of the lung has been reported in a 45-year-old alcoholic, homosexual man with AIDS.⁶

In addition, certain unusual neoplasms, such as clear cell renal carcinoma⁷ and primary bile duct lymphoma,⁸ have been reported in association with AIDS. Immunodeficiency and the cytopathogenic effect of certain viral infections which occur in AIDS patients have been implicated as possible factors in the genesis of malignancy. There is believed to be an association of Epstein-Barr virus infection with the development of lymphoma in AIDS patients.⁹ A possible relationship between the development of malignancy and stem cell

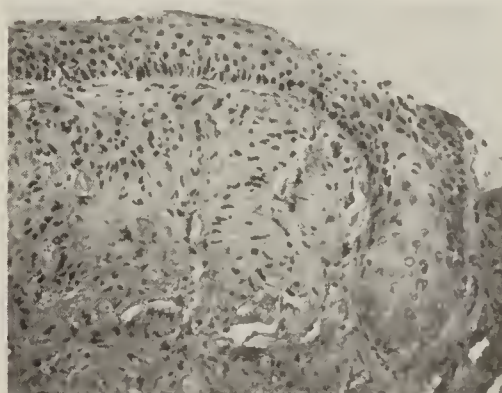


FIGURE 2. Section of a biopsy of endobronchial tumor showing metaplastic mucosa overlying submucosal granular cell tumor. (hematoxylin-eosin stain; original magnification $\times 200$).

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damage caused by cytomegalovirus infection has been described, and hepatitis B virus, which frequently coinfects patients with HIV, has been associated with hepatocellular carcinoma.⁸

In view of these findings, it seems possible that the abnormal immune status and frequent viral infections that occur in patients with AIDS may alter the clinical course of certain neoplastic diseases or even play a direct role in the genesis of tumors.⁸

Granular cell myoblastoma is known to occur in the presence of several conditions associated with abnormal cell-mediated immunity. These include sarcoidosis and all major histologic types

of bronchogenic carcinoma.⁹

It thus seems possible that the altered immune status of this patient may have contributed to the development of multiple granular cell myoblastomas. This is an association which has not, to our knowledge, been previously reported.

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Multiple carcinomas of the large bowel in chronic ulcerative colitis

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The development of adenocarcinoma of the colon has long been recognized as a complication of chronic ulcerative colitis, particularly in patients who have involvement of the entire colon, a long history of the disease, or a chronic, continuous pattern of symptoms.^{1,2} We describe a patient with longstanding chronic ulcerative colitis who presented with an acute exacerbation of his disease complicated by the presence of multiple carcinomas.

CASE REPORT

A 39-year-old man was admitted to Long Island Jewish Medical Center complaining of abdominal pain, rectal bleeding, increasing weakness, and a 40-lb weight loss. At the age of 23 he had experienced severe diarrhea which was diagnosed as ulcerative colitis. He was treated with sulfasalazine and a preparation of psyllium hydrophilic mucilloid with moderate success. Colonoscopy at the age of 33 revealed two polyps at the splenic flexure, one of which was malignant on biopsy. The patient was advised to undergo total colectomy but refused.

For the next six years the patient was

treated by a nutritionist with vitamins and a high fiber diet. He then presented to another hospital with fever, diarrhea, weight loss, and anemia. Flexible sigmoidoscopy showed an inflamed mucosa, multiple pseudopolyps, and a large sessile polypoid mass at 14 cm. A barium enema revealed an extensive area of irregular thickening of the lateral wall of the ascending colon over an area of approximately 10 cm consistent with malignant infiltration. It also revealed an area of irregularity and narrowing of the splenic flexure suggestive of a second carcinoma (Fig 1). The terminal small bowel showed changes of reflux ileitis, with narrowing and irregular-

ity and loss of mucosal folds. A computed tomographic (CT) scan confirmed the presence of an infiltrating lesion of the lateral wall of the cecum and ascending colon; the liver appeared normal (Fig 2). The patient was treated with steroids, antibiotics, transfusions, and parenteral hyperalimentation, and he was admitted to this institution for definitive surgery.

On examination, the patient was pale, anxious, and emaciated, with marked edema of the lower extremities. He had mild diffuse abdominal tenderness, with no distention or masses. Laboratory studies included a hemoglobin of 8.5 g/dL; hematocrit, 25%; serum albumin, 1.9 g; and carcinoembryonic antigen (CEA) level, 80 units. Sigmoidoscopy confirmed the presence of an infiltrating carcinoma at 18 cm. After a ten-day course of hyperalimentation and multiple transfusions, the patient underwent a complete proctocolectomy with ileostomy. Operative



FIGURE 1. Barium enema showing tumors involving the ascending colon and splenic flexure.

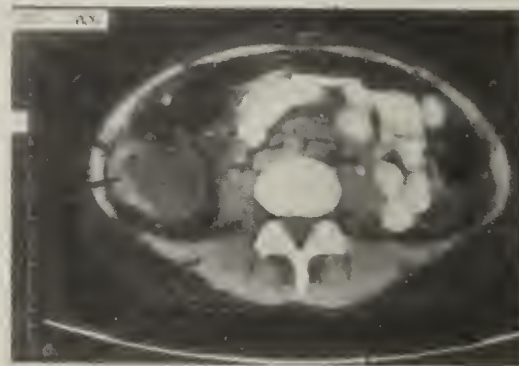


FIGURE 2. Computed tomographic scan demonstrating infiltration of the lateral wall of the ascending colon.

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findings included a 10 × 10-cm mobile carcinoma involving the ascending colon, a 12 × 14-cm mass in the splenic flexure and descending colon, and a thickened colon throughout. The mesentery of the colon and small bowel contained multiple soft enlarged lymph nodes. The liver and peritoneum appeared to be free of metastases. The ileum was divided approximately 10 cm from the cecum and was noted to be edematous, granular, and hyperemic—consistent with backwash ileitis.

Following surgery, the patient did well and was discharged on the 13th postoperative day. Six weeks after discharge he had a low grade fever and vague abdominal complaints. A CT scan showed multiple liver metastases confirmed by needle biopsy. The patient received a course of chemotherapy with 5-fluorouracil and leucovorin, but died two months later.

Study of the surgical specimen showed that the mucosa of the entire colon was diffusely hemorrhagic and inflamed, with multiple patchy areas of ulceration and multiple pseudopolyps. Three separate cancers were identified grossly. One tumor in the cecum measured 10 × 6 cm, and a second at the splenic flexure measured 11 × 10 cm. Both showed a flat, ulcerated mucosal surface and deep penetration of the colonic wall. The third cancer was a polypoid 2.5 × 2.5-cm lesion in the sigmoid colon. There was additionally a dramatic papillary transformation of the mucosa, distal to the cecal cancer and on either side of the splenic flexure cancer. Microscopic examination of the cecal and splenic flexure cancers showed adenocarcinoma with a prominent colloid component infiltrating the entire colonic wall into the serosal fat (Fig 3). The sigmoid colon cancer extended only into the submucosa. Sections from villous-appearing mucosa showed villoglandular changes with se-

vere dysplasia (Fig 4), an adenomatous polyp with a microscopic focus of intramucosal adenocarcinoma, and a polypoid adenocarcinoma. Multiple sections from different areas of colon and rectum showed active ulcerative colitis with various grades of dysplasia. Backwash ileitis was also noted. Forty-three lymph nodes from colonic mesentery were negative for metastatic carcinoma.

DISCUSSION

Synchronous carcinomas of the large intestine have been reported in approximately 2–3% of patients presenting with colon cancer.^{3–6} Metachronous cancer develops after partial colon resection in an additional 5% of patients.^{7–9} Predisposing causes for the development of multiple synchronous carcinomas include familial multiple polyposis (FP) and ulcerative colitis (UC). The proportion of multiple synchronous carcinomas has been reported as 8–43% for colitis and 25–44% for polyposis.³

The patient described here was unique in that he was essentially untreated for six years after being diagnosed as having colon cancer. At operation, the colon manifested the entire spectrum of disease, from various degrees of pre-malignant changes to frank carcinomas with progressive levels of infiltration.

In patients with idiopathic colon carcinoma, the tumors are found predominantly in the left colon and rectum, whereas in those patients with UC and FP, the carcinomas appear to be more evenly distributed throughout the entire colon.^{1,10} Tumors in colitis are often flat and deeply infiltrating. The dysplasia in ulcerative colitis is recognized not only by its characteristic microscopic features but also by the macroscopic findings of elevated villous-appearing mucosa or discrete polyps. The latter should not be confused with the more common inflammatory pseudopolyps which present as small filiform or rounded shiny polyps. Removal of the polyp may be required to establish the

diagnosis. In patients with ulcerative colitis, the proportion of poorly differentiated and colloid carcinomas is higher than for those tumors that arise in non-colitic patients.¹¹

A number of reports in the literature have examined the relationship between chronic ulcerative colitis, multiplicity of colon tumors, and long term survival in colon cancer. Several large studies have examined the prognosis for single colon tumors in colitic compared to non-colitic patients and have clearly shown that there is no significant differences in survival when the patients are properly matched for stage of the disease.^{7,12,13} The five-year survival for patients with carcinoma and ulcerative colitis ranges from 40% to 45%, which is similar to the overall survival in colorectal carcinoma.^{14–16}

Survival in multiple synchronous tumors has also been studied, but in smaller numbers of patients and usually in those patients without colitis. The five-year survival appears to be as good in patients with two or more synchronous carcinomas as in those with a single tumor; it ranges from 40% to 49%.^{4,5,17}

There is little information available regarding the survival of patients who have a combination of multiple synchronous tumors and chronic ulcerative colitis. Although previous studies indicate that ulcerative colitis and multiplicity of tumors do not independently affect survival, the combination of both may well worsen the prognosis. The outcome in this case would tend to support this.

In summary, the prognosis for carcinoma of the colon does not appear to be independently affected by the presence of multiple tumors or chronic ulcerative colitis. Both factors together may adversely affect survival, although the number of recorded cases does not permit a definitive conclusion.

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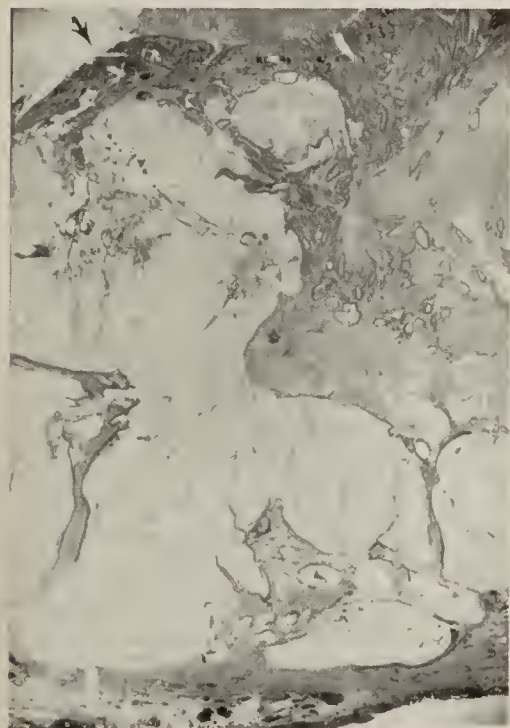


FIGURE 3. Adenocarcinoma infiltrating colonic wall. Note prominent colloid component (arrow at mucosal end).

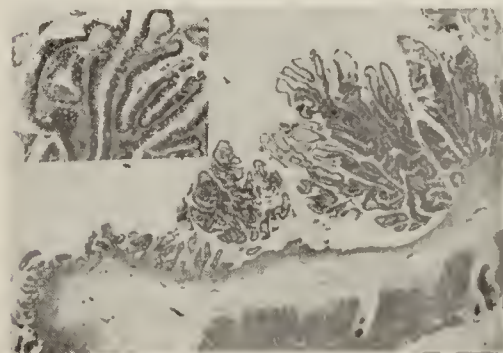


FIGURE 4. Villotubular change with severe epithelial dysplasia.

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The use of prophylactic desmopressin (DDAVP) in labor to prevent hemorrhage in a patient with Ehlers-Danlos syndrome

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Ehlers-Danlos syndrome (EDS) is a genetically inherited group of disorders with at least eight subtypes, all having increased joint mobility and connective tissue compromise in common. The pattern of inheritance and the nature of risks in pregnancy varies with the type of disorder.^{1,2} Antepartum or postpartum hemorrhage is a major risk for some pregnant patients with this syndrome, particularly with types I and IV. We present here a patient with Ehlers-Danlos type III with a major hemorrhagic component who was successfully treated with desmopressin (DDAVP) and had a vaginal delivery at term.

CASE REPORT

The patient is a 28-year-old white female, gravida 2 para 0010, with a long history of excessive bleeding. The patient had a history of irregular and very heavy menstrual periods for which she had had seven dilation and curettage procedures. Her bleeding was finally controlled by monthly daily injections of DDAVP during her menses. The patient underwent an ovarian cystectomy and appendectomy at age 18; this resulted in excessive bleeding, and she required a transfusion. Dental procedures were complicated by increased bleeding until she began receiving prophylactic DDAVP before each procedure. The patient was seen prior to conception, and was counseled regarding the major risks of pregnancy with Ehlers-Danlos syndrome.

The initial diagnosis of EDS was suggested by laxity of the joints, easy bruising, multiple ligamentous injuries of the ankle, knee, and elbow, and a separated collarbone. The patient had a history of incapacitating migraine, occasionally resulting in syncope. After the clinical features of her disease were evaluated, she was given the diagnosis of EDS type III by the genetics department of a leading university hospital. The patient was one of ten siblings, with no other affected relatives.

The patient's clotting disorder was thought to be functional, with abnormal stimulation of platelets by collagen. Von Willebrand factor levels were borderline normal.

The patient progressed well during the pregnancy with the exception of worsening migraines. The patient did have abdominal striae. At 42 weeks, with the cervix in good position, labor was induced in the hopes of avoiding a precipitous delivery. Baseline bleeding times during pregnancy were elevated at ten minutes on two occasions. The patient responded well to oxytocin. At 4-5 cm dilation, the oxytocin was discontinued, and a half hour later 20 mg of DDAVP was given. There was a slightly increased frequency of contractions. The fetal heart rate was stable and normal. Post DDAVP bleeding time was six and a half minutes. The patient had a normal vaginal delivery over a median episiotomy without extensions, during which blood loss was normal. The active phase of labor lasted five hours, and the second stage lasted two hours. On postpartum days one and two the bleeding times were seven and nine minutes, respectively. However, on postpartum days three, four, and five, the bleeding times were 10, 16, and 12 minutes, respectively, requiring daily DDAVP.

On postpartum day two, the patient began to have slightly more than average

bleeding, but the hematocrit remained stable at above 30%. She was discharged on postpartum day five. Von Willebrand factor rose from about 60-70% before conception to 211% on postpartum day one, probably resulting from a combination of pregnancy and DDAVP.

DISCUSSION

Because of the rarity of this syndrome, recommended management in pregnancy is unclear. Some authors suggest that in severe forms, such as type IV, cesarean section be performed before labor.³ Others suggest that the delivery mode be determined by Ehlers-Danlos type and patient profile.^{1,4,5} We believe that either vaginal delivery or cesarean section may represent a major risk in these patients, and that the mode of delivery should be individually based on the patient's condition and obstetric indications.

Although these patients are more likely to have preterm labor, an incompetent cervix, preterm rupture of the membranes, and hernias,^{1,2} this patient suffered none of these. Her development of abdominal striae may have been a good prognostic sign, as they are more likely to be absent in the most severe forms.¹ Consideration was given to prophylactic cerclage, but because of the basic defect, we felt that suturing a collagen-deficient cervix could have a greater risk than benefit. Since up to 50% of pregnancies are delivered prematurely,³ modified bed rest and frequent cervical examinations seem reasonable precautions. Labor may be

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rapid due to a lax cervix and, because these patients may have catastrophic perineal tears, attention must be paid to the early signs of labor in order to allow for a controlled delivery.

The high incidence of preterm rupture of the membranes may be due to either maternal or fetal disease. Since 78% of patients with Ehlers-Danlos syndrome were themselves delivered prematurely secondary to rupture of the membranes,¹ a fetal factor is plausible. It is important to recognize this in view of advancing reproductive technology. Because of the high maternal risks involved in pregnancy and delivery, the possibility of oocyte donation and embryo transfer to one of her sisters was discussed with this patient and rejected. However, in view of the possibility of fetal contribution to pregnancy complications, there are still attendant risks associated with this concept. Not all EDS subtypes are associated with coagulopathy, which is unusual in type III EDS. However, because of this potential problem, all patients with EDS should probably be screened for bleeding times.

Type III EDS, also described as benign hypermobile EDS, is characterized by arthritis and joint laxity. It is an autosomal dominant condition. In view of the patient's family history, her condition most likely resulted from a spontaneous mutation.

Our review of the literature found no

reported cases in which DDAVP was used during labor. Weinbaum et al³ report the use of DDAVP prior to cesarean section in a non-laboring patient with Ehlers-Danlos syndrome type IV. Theoretically, DDAVP increases the risk of uterine hypercontractility. As a precaution, we therefore discontinued oxytocin stimulation one half hour before giving the DDAVP. Although there was a slight increase in the rate of contractions, hypertonicity was not noted, and the fetal heart rate remained normal during and after the infusion.

DDAVP releases factor VIII from endothelial cells, which aids in platelet adhesion. Repeated use of DDAVP at less than 24-hour intervals is therefore ineffective, as the cells are depleted. DDAVP also has a positive effect on clotting on both platelets and the vessel wall. Efficacy does not depend on low concentrations of factor VIII. There is, however, an increase in factor VIII and platelet adhesion in all patients regardless of the etiology of the clotting disorder (except types II A&B von Willebrand's disease). The use of DDAVP may therefore also be valuable in other clotting disorders in pregnancy. In fact, in patients with normal clotting studies undergoing open heart surgery, blood loss may be reduced by preoperative use of DDAVP.⁷

This patient's bleeding time was significantly decreased by DDAVP. Interestingly, her baseline bleeding time was

much worse postpartum than during the pregnancy. There is no easy explanation for this finding, as factor VIII remains high in the immediate puerperal period.

We agree with Smith and Phelan⁵ that in this rare condition, rather than generic recommendations for this diverse disease, individual treatment is essential, and that vaginal delivery is possible in selected cases. New advances in pharmacology and in reproductive technology raise interesting new possibilities in the care of these patients.

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Address correspondence to Editor, New York State Journal of Medicine, 420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication after editorial review. All letters are personally acknowledged by the Editor.

Crack abuse and asthma

TO THE EDITOR: After reading the case report of Rao et al¹ on crack abuse and asthma in the October 1990 issue of the *Journal*, I would like to comment on several aspects of this case which warrant further discussion.

The asthmatic patient described presented with a severe metabolic acidosis with an inadequate respiratory response. This was presumably due to status asthmaticus for which he was treated with bronchodilators. Although asthmatics with status asthmaticus more commonly present with a respiratory acidosis, these patients can certainly have a lactic acidosis. This results from their increased work of breathing and poor peripheral tissue oxygenation.² However, this asthmatic patient had a respiratory rate of only 26 and no pulsus paradoxus, certainly not suggestive of severe status asthmaticus. Could his metabolic acidosis have been the result of some other pathology? Was an SMA6 and other chemistries done to help determine the cause of this acidosis? Were repeat arterial blood gases done after his bronchospasm improved and prior to his discharge from the emergency room?

Even assuming for the moment that his acidosis was secondary to asthma, were any objective parameters of his airflow obstruction obtained? Was spirometry or a peak flow done prior to his discharge? Unfortunately, how patients feel often does not correlate with the extent of their airflow obstruction.

Finally, why was this patient not discharged on a short course of steroids or even given any steroids in the emergency room? Recent studies clearly demonstrate the need to treat the anti-inflammatory component of asthma.^{3,4} Any patient with asthma severe enough to cause a pH of 6.98 should probably be admitted to the hospital. If not, at the least he should be given a course of steroids in addition to other bronchodilators.

I suspect the deficiencies that I have pointed out reflect merely the abbreviated nature of the "case report" format. However, in my opinion, leaving the

case report incomplete in this manner is incorrect and misleading to readers.

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In reply. The patient described in our report was first seen in the emergency room where he complained of shortness of breath. He was treated and released by the emergency room physicians. Follow-up SMA6 and blood gases were not done prior to discharge, apparently on the basis of clinical evidence of recovery, including improved spirometry measurements.

Not having been involved in the care of this patient at that stage, I am unable to answer the questions regarding the decisions not to initiate steroid therapy and not to admit the patient to the hospital.

Later, the patient was admitted to my care after unsuccessful cardiopulmonary resuscitation, following his second entry to the emergency room.

Dr Mermelstein's comments regarding lactic acidosis are acknowledged.

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Rural obstetric care

TO THE EDITOR: The lowest neonatal mortality rates (NMR) are found in small maternity units which practice low technology obstetrics for low risk mothers, and which refer high risk mothers to level 3 perinatal centers for delivery where newborn intensive care is immediately available. This is sug-

gested by Rosenthal et al¹ in their article presenting data from rural Western New York State in the November issue of the *Journal* and is supported by data from upstate Eastern New York.² Rural New York hospitals should not congratulate themselves, however, until their NMRs are at or below two per thousand²⁻⁵ and no mother is required to travel more than 45 minutes to have a baby under medical supervision.⁶ To achieve these goals several points must be emphasized:

Personal care and a friendly environment are extremely important for the mother and the fetus.^{5,7}

Unproved technology or inappropriate application of otherwise useful technology will increase their risks.^{8,9} Newborn intensive care units embody some of the most valuable components of modern perinatal technology.¹⁰

The halfway technology implemented in some level 2 perinatal centers does more harm than good.^{11,12}

In choosing the place of delivery there is a delicate balance between the risk status of mother and fetus, the size and expertise of the maternity unit, and travel time. In rural areas, compromises are necessary, but all three of these factors must be considered.^{12,13}

We are learning that competition does not necessarily improve services or reduce costs. This lesson is especially poignant in the area of perinatal care where hospital geopolitics has forced some mothers to travel long distances and submit to unproved technologies in an unfamiliar setting, when their babies could have been delivered closer to home with greater safety.¹¹⁻¹³

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In reply. Dr Cunningham has helped to expand our concept of prenatal care by his excellent review of our article with a focus on the perinatal care of infants. We would like to focus on a few of his comments.

Halfway technology implemented in some perinatal centers may very likely do more harm than good. We believe as a point of our argument that birthing care does not necessarily have to take place in a “hi-tech” center but high tech care must be connected and available by a previously negotiated agreement. In our article we specifically stated that family physicians should not attempt to provide high risk obstetric services and that a small hospital should not attempt to deliver all levels of perinatal care. When a rural center participates in a regional network it is the responsibility of both the rural center and the regional center to collaborate on the training and implementation of a quality neonatal stabilization program.

We would take exception to Dr Cunningham’s suggestion that in rural areas compromises are necessary. We believe that in a well-coordinated regional system rural clients can expect care equivalent to that received by urban clients and should hold their institutions to those standards. In fact, as Dr Cunningham suggests, birthing that occurs in a personal and friendly environment with the appropriate application of technology in association with a region-

al system should lead to equality of care.

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Involvement of physicians in capital punishment

TO THE EDITOR: A report entitled “Physician involvement in capital punishment,”¹ prepared by the Committee on Bioethical Issues of the Medical Society of the State of New York, appeared in the January 1991 issue of the *New York State Journal of Medicine*. This report vigorously opposes physician-assisted lethal injection as a method of execution. I would like to make it clear that this opinion is not universally held by all physicians, and in fact may not even be a majority opinion.

Rather than providing an even-sided discussion of the moral issues involved, the report inserts issues with no relevance to the stated topic. Many paragraphs are spent denouncing physician involvement in state-sponsored torture, medical experimentation in Nazi concentration camps, and Nazi euthanasia. What do these topics have to do with the United States except to inflame passions against capital punishment? Let us be rational! Murderers in the United States, ready for execution after years of appeals to state and federal courts, are not political prisoners in Tibet. These convicts have been duly sentenced under the laws of a free, open, and democratic society.

I suspect that the opposition of this committee is actually not based on the idea that physicians are restrained by the Hippocratic Oath. Rather I believe that there is a hidden agenda. This group is actually opposed to capital punishment despite its early disclaimer. Thus the statement, “. . . the overwhelming view of doctors and medical associations is that ‘physician participation in any phase of the death penalty is not permissible by medical ethical standards.’”

Here finally the real agenda surfaces. Not only does this committee declare it unethical for a physician to lethally inject the convict, it now extends the definition of unethical conduct to include “participation.” And what is participation? Among other things, “the deter-

mination of mental and physical fitness for execution.”

The committee states, in its final sentence, that the moral authority for its report is based on the statement *Primum non nocere*. I would submit as my moral authority allowing executions, the Pentateuch and the United States Supreme Court.

No arguments are likely to change individual beliefs regarding the propriety of capital punishment. This committee report, using the smokescreen of torture, concentration camp experimentation, and euthanasia, should be seen for what it truly is. There are those of us, physicians included, who believe that some murderers have forfeited the right to live and deserve to die. I would argue that physicians have the moral responsibility to use their special skills to help solve societal problems.

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1. Rosner F, Halpern AL, Kark PB, et al: Physician involvement in capital punishment. *NY State J Med* 1991; 91:15–18.

TO THE EDITOR: The report, “Physician involvement in capital punishment,” by the Committee on Bioethical Issues of the Medical Society of the State of New York (MSSNY) provided a thoughtful overview of the ethical dilemma facing physicians who might become involved in death penalty cases.¹ Regrettably, the MSSNY policy statement on physician involvement in the trial and execution of a human being did not follow up this report by clearly proclaiming that a psychiatrist should not treat a mentally incompetent prisoner condemned to death, if said treatment would advance the execution of the prisoner.

The Committee Report refers to Sargent’s² complete opposition to psychiatric involvement and also mentions that Clare³ urged “doctors to articulate and implement ethical codes that unambiguously prohibit doctors from participating in executions . . .” Why, then, has no position been put forward in the policy statement on psychiatric treatment of a prisoner condemned to death?

The only guidance provided is that it is permissible for a physician to “relieve acute suffering of a convicted prisoner while he is awaiting execution.” However, the US Supreme Court ruling in *Ford v Wainwright*,⁴ that a mentally incompetent person cannot be executed, supplies a means by which psychiatrists

can prevent the execution of the mentally ill prisoner, namely by not treating him to the point where he is competent for execution. By refusing to administer therapy beyond that which is necessary to relieve acute suffering, pressure will also be placed on the government to commute the sentence to life in prison without hope of parole, if there is an interest in such care for the prisoner.

This position might not seem to be just, but the broader ethical issues must be kept in focus: as long as there is a foothold from which to combat the state sanctioned execution of a person, it is every physician's duty to his patient and to the well-being of others facing a similar future to take advantage of this opening and, thus, contribute to the saving of lives. The MSSNY has such an opportunity, and accordingly it should adjust its policy statement on capital punishment. The Committee Report referred to the Hippocratic Oath's opposition to lethal injection. The Oath also affirms that, "In every house where I come I will enter only for the good of my patients, keeping myself far from all intentional ill-doing . . ." If a doctor's duty lies in the well-being of his patient, then surely it is better not to treat the mentally ill prisoner, rather than help him regain competency for his execution.

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In reply. Dr Minkin misrepresents the position of the Committee on Bioethical Issues of the Medical Society of the State of New York. Many of the committee members including the chairman are personally strongly in favor of capital punishment. Our paper clearly states that it "is concerned with the physician's role or lack thereof in a society in which the criminal justice system includes capital punishment." Our essay takes no position on the societal-legal issue of whether or not capital punishment should be part of the criminal justice system.

Physician involvement in state spon-

sored torture and Nazi physician experiments are examples of circumstances where physicians violated fundamental principles of medical ethics. Our essay states that we believe it is also unethical for a physician who is dedicated to the preservation of life and the healing of disease to participate even in a legally authorized execution.

We repeatedly assert throughout our essay that we do not directly address the morality or immorality of the death penalty. An individual's position on capital punishment is the personal moral decision of the individual. We also present views of physicians who differ with our position and believe that it is not immoral for a physician to give the lethal injection in a case of capital punishment. We have no hidden agenda.

Mr Halpern makes a valid point. An individual psychiatrist may well refuse to treat a mentally incompetent prisoner condemned to death so that he becomes competent for execution. The policy statement of the Medical Society of the State of New York published in our article, which argues against physician assisted lethal injection as a method of execution, is consistent with the Principles of Medical Ethics of the American Medical Association (AMA) and the American College of Physicians (ACP). In late 1990, the ACP adopted a resolution calling on the AMA to "reaffirm, clarify and publicize its position that it is unethical for physicians, regardless of their personal views on capital punishment, to participate in legally authorized executions, except to determine or certify death."¹ In December 1990, the AMA House of Delegates, meeting in Orlando, Florida, approved a resolution reaffirming and strengthening its 1980 statement prohibiting physician participation in executions. The new resolution mandates the AMA to notify all state licensure and certification agencies that it considers physician participation a serious ethical violation.

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1. Charnow J: College view on executions wins quick AMA adoption. *Observer* 1991; 11:3.

Impact of the Great War on the medical community

TO THE EDITOR: Thank you for pub-

lishing Dr Haller's timely article, "The Great War: Its impact on the British and American medical communities, 1914-1918," which appeared in the January issue of the *Journal*.¹ The war in the Persian Gulf evokes images of the Great War scenario. I sincerely hope that this article stimulates serious consideration by the medical community of the preventive aspects of our military engagement in the Middle East.

Another area of concern is Dr Haller's statements in the article attributing the discovery of smallpox vaccine to Jenner in 1796. William McNeill, in his book *Plagues and Peoples*, writes that the practice of smallpox inoculation was introduced into England in 1721 and by Catherine the Great into Russia in 1768. In 1775 Frederick II of Prussia introduced inoculation into his kingdom and in 1776 George Washington ordered it for all his soldiers.² I hope that Dr Haller will be able to resolve this discrepancy for me.

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In reply. Edward Jenner (1749-1823) of Gloucestershire introduced preventive inoculation in 1796 after observing that dairymaids who had contracted cowpox through milking did not fall victim to the scourge of smallpox. With the encouragement of John Hunter, he performed a *vaccination* on James Phipps, using attenuated matter collected from the arm of a milkmaid who had contracted cowpox. The immunization proved effective and, after testing his thesis 23 more times, he published *An Inquiry Into the Causes and Effects of the Variolae Vaccinae* (1798).¹ The merit of Jenner's work lies in its experimental nature, his testing of a thesis, and his giving validity to a cure previously based on little more than anecdotal information.

Jenner's notoriety for vaccination should not be confused with *variola*, which was used by many scientific predecessors to Jenner. Variolation involved the inoculation of the virus of unmodified smallpox to produce immunity. The practice extends far back into Oriental medicine, wherein the dried crusts of smallpox lesions were applied to the skin or nasal membranes, or even ingested. In England, one finds refer-

ences to inoculation in the communications to the Royal Society as early as 1713. In 1718, Lady Morey Wortley had her son inoculated in Turkey, and in 1721, Zabdiel Boylston of Boston inoculated his son and two slaves during an epidemic of smallpox.

Perhaps the best work on variolation was written by Arnold Klebs (*Die Variolation im achtzehnten Jahrhundert*) in 1914.² In it, he divides the history of variolation into an introductory period (1713–1721), stagnation (1727–1746), revival (1746–1764), and experimental (1764–1798). In Europe, the practice was first introduced by Emanuel Timoni and Pilarini whose published accounts in 1713 and 1716 led to extensive inoculations of children in Boston, Charleston, and among populations in England and Scotland. Doctors attenuated the virus by passing it through several human subjects by means of an arm-to-arm method, or by dilutions in water. By the 1760s, doctors were experimenting with inoculation by puncture.

The success of Jenner's vaccination technique soon relegated variolation to the dustbin of Western medical practice. In fact, by 1840, Parliament had even passed a law declaring its continued practice a felony. However, as a preventive measure, the practice continued in many Third World countries with examples of its use occurring into the 1970s.^{3–6}

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Physicians and the media

TO THE EDITOR: Physicians are confronting a more complex world in which the need to get their message before the public becomes increasingly important. The major conduits are the broadcast and print media. Like many other interest groups, physicians have developed a love-hate relationship with the fourth estate. When information is publicly released which is favorable or “balanced,” physicians are pleased but seldom share their satisfaction with journalists. If, however, they sense “doctor bashing” or an unfair playing field they are not reticent sharing their displeasure. Bad news seems to get more attention than good.

As physicians, we like to think we know what is relevant, and find uncomfortable the fact that it is the journalists who will decide what is newsworthy. We may control the source, but they control dissemination. Complicating many an issue is the convergence of a series of players including legislators, physicians, consumers, and other interest groups. It is often left to the press to untangle complex problems. It is here that physicians can assume a very important role in clarifying and shaping a communication. The emphasis is often on simplifying and identifying its impact on patients and physicians. The

press and electronic media must constantly ask of themselves whether each topic is of importance and interest to their readers or listeners. In this search, the representatives of the media seek out leaders who can succinctly speak on the issue. The press can often devote a great deal of time to developing a story and thus they diligently search for information. Programs such as the evening television and radio news seem to go for the quotable “sound bites.” The time constraints within which they operate are stringent. Exceptions to these are the review and analysis programs on public television, and the expanded network news programs.

This news communication world is somewhat removed from that of the physician but is one that is looming larger all the time. There is a need for prepared physician speakers and communications specialists. Physicians could be trained to use communication skills effectively. The communication specialist could be a professional who prepares the speaker for specific encounters and encourages interaction with responsible media sources. From time to time, the Medical Society of the State of New York has prepared individuals to act as spokespersons. In place of an ad hoc policy, this should be a planned endeavor with adequate resources and a commitment to make it work.

The need to develop media strategies and shape communication is a must if we are to meet the challenges of an ever-changing society. Other groups have become adept at understanding and working with the media. We cannot afford to do less.

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Cardiac surgery research results encourage improvements in performances

The quality of cardiac surgery in hospitals in New York State is the subject of a scientific paper in a recent issue of the *Journal of the American Medical Association (JAMA)*.¹ The study, using data from the first six months of 1989, was authored by members of the New York State Department of Health.

The purposes of the study were to determine the set of significant clinical risk factors related to cardiac surgery death or survival and to identify cardiac surgical centers most likely to have quality-of-care problems. The precise patient risk factors identified by the study permitted researchers to calculate a hospital risk-adjusted mortality rate, based on the pre-operative condition of the patients. The resulting comparison among hospitals, therefore, takes into account the differing complexity of cases treated by different facilities. The severity measures are the most sophisticated yet available and were developed by New York State's Cardiac Advisory Committee, which includes clinicians from cardiac surgery centers in New York and other states.

Patient Risk Factors

The study showed that higher probabilities of death were associated with increased age, female gender, a myocardial infarction in the week preceding the operation, diabetes, dialysis dependence, unstable angina, congestive heart failure, more than 90% narrowing of the left main trunk, and disasters (for example, acute structural defect, renal failure, cardiogenic shock, gunshot). The odds ratios for each of the risk factors, except age, are displayed in Table I. The odds ratio is an estimate of the odds of a patient with a risk factor dying, divided by the odds of a patient without the risk factor dying, holding all other risk factors constant.

Uses of Data

For each hospital performing open heart surgery in New York State from January 1989 through June 1989, the number of cardiac surgical patients, the crude mortality rate, the expected mortality rate and upper and lower bounds for the expected mortality rate were calculated. In fall 1989, the composite data were given to all 28 hospitals certified to perform adult open heart surgery in New York State. The information derived from these data was in-

TABLE I. Significant Risk Factors* Related to Cardiac Surgery Death or Survival

Significant Risk Factors	Odds Ratio
Age	
Female gender	1.28
Reoperations	
1	2.55
2 or more	5.06
Ejection fraction	
20-39%	1.51
Less than 20%	3.41
Previous myocardial infarction	1.94
in last 7 days	
Diabetes	2.08
Dialysis dependent	3.21
Disaster	7.55
Unstable angina	2.01
Congestive heart failure	2.45
More than 90% narrowing of	1.81
left main trunk	
Valve operation	1.92
Other operation (not coronary	5.62
artery bypass graft or valve)	

* All variables shown are significant at least at the 0.05 level.

tended to stimulate these hospitals to inquire into the cause of their outcomes and to identify ways to improve their performance. The primary purpose of this ongoing effort is to promote a continuing improvement in the quality of care received by patients with coronary artery disease in New York State. A recent industry newsletter article praised the study when it stated, "The study is considered an instrument of major importance in quality assurance. The data base and its tested methodology provide a benchmark for a hospital to evaluate the performance of its cardiac surgery program."²

Health Department follow-up investigations identified areas where changes in policies and procedures at hospitals were most likely to improve statistical records. Twenty of the 28 hospitals performing surgery in the first six months of 1989 improved their performance during the first half of 1990. The 1989 and 1990 hospital-specific data are shown in Table II.

Study Results

For all open heart surgery, the statewide mortality rate declined from 4.87% in the first six months of 1989, to 4.18% in the same period of 1990. This decline of 14% took place even as the average severity of cases being treated increased. For coronary artery bypass grafts (the most common procedure), the statewide mortality rate declined from 3.59% in the first half of 1989 to 3.03% in the same period of 1990, a decline of 16%.

Each of the hospitals was also given a computer diskette that allowed it to calculate the risk of death for patients with any combination of clinical conditions found in the study to be significant. Hospitals were also given the

TABLE II. Crude and Risk-Adjusted Mortality Rates for Hospitals Performing Adult Cardiac Surgery in New York State, Discharged January–June 1989, January–June 1990

Hospital	1989		1990	
	Crude Mortality Rate	Risk-Adjusted Mort. Rate	Crude Mortality Rate	Risk-Adjusted Mort. Rate
Mount Sinai Hospital	3.42	2.30	3.26	2.13
Lenox Hill Hospital	3.29	2.33	5.29	3.71
Presbyterian Hospital—City of New York	3.86	2.74	3.44	2.96
Westchester County Medical Center	2.23	2.79	4.48	5.99
Long Island Jewish Medical Center	4.29	3.41	2.17	2.23
Buffalo General Hospital	2.93	3.72	3.79	5.04
New York University Medical Center	4.52	3.94	4.16	3.02
St Francis Hospital	4.30	4.19	3.09	3.03
Albany Medical Center Hospital	3.66	4.27	6.41	5.75
New York Hospital	4.44	4.34	3.43	2.82
University Hospital (Stony Brook)	8.65	4.53	4.29	2.91
State University Hospital Upstate Medical Center	4.62	4.87	5.91	7.60
Binghamton General Hospital Division	3.61	4.88	2.75	2.99
North Shore University Hospital	4.78	5.13	7.99	6.50
Bellevue Hospital Center	7.41	5.22	6.98	4.91
Montefiore Medical Center-Weiler Hospital	7.48	5.26	3.28	2.54
Rochester General Hospital	6.11	5.38	3.29	4.92
Maimonides Medical Center	6.30	5.48	3.61	2.75
Strong Memorial Hospital	5.34	5.98	7.83	8.35
Millard Fillmore Hospital	5.06	6.15	4.55	6.41
Montefiore Medical Center—Moses Division	5.70	6.22	2.85	3.12
St Joseph's Hospital Health Center	3.70	6.46	3.51	4.31
St Luke's Roosevelt Hospital—Manhattan	4.65	6.82	6.77	5.96
St Vincent's Hospital and Medical Center	9.90	8.01	1.68	2.09
University Hospital of Brooklyn	7.64	9.64	5.48	5.95
Arnot-Ogden Memorial Hospital	6.77	9.70	4.10	4.71
Winthrop-University Hospital	7.33	10.06	2.92	4.14
Erie County Medical Center	14.29	17.89	3.23	9.20

1989 Statewide Crude Mortality Rate = 4.87%.

1990 Statewide Crude Mortality Rate = 4.18%.

means to calculate the volume of cases, risk factors and risk-adjusted mortality rates for their individual surgeons.

Implications

Patients considering cardiac surgery should discuss this new information with their physicians, particularly their cardiologists, who provide most cardiac surgery referrals. Patients and referring physicians are expected to use this information to assist them in making decisions on the choice of institutions for cardiac procedures. The Department will publish periodic updated data on this subject. Patients should be able to obtain from their doctor or hospital:

- the performance history of each hospital;
- the performance record of individual surgeons;
- the risk of mortality for patients based on their individual risk factors.

Availability of these new cardiac surgery data is expected to foster development of a new pattern for the use of information in patient decision-making in other areas of medicine as well.

Research conducted at the New York State Department of Health and elsewhere also indicates that hospitals and physicians performing more than a limited volume of a particular surgical procedure, such as cardiac surgery,

have better outcomes. While the evidence suggests that high volume surgery programs have overall lower mortality rates, lower volume programs can also have good records.

The New York State Department of Health emphasizes that patients and physicians should use extreme caution in making judgments based on small numbers of cases. Just one or two cases can cause wide swings in the average of a physician or hospital doing only a small number of cases.

The Health Department expects to host a conference later in 1991 for those involved in referral of patients for cardiac surgery, as well as for those directly involved in cardiac surgery to foster continuing improvements in quality. This conference will make extensive use of the data presented in this study.

For more information regarding the study, contact: New York State Department of Health, Office of Health Systems Management, Bureau of Health Care Research and Information Service, 2019 Corning Tower, Albany, NY 12237.

References

1. Hannan EL, Kilburn H, O'Donnell JF, et al: Adult open heart surgery in New York State: An analysis of risk factors and hospital mortality rates. *JAMA* 1990; 264:2768–2774.
2. Read cardiac surgery data with caution. *NY Hospital & Health News* 1990; 11(12):1,3.

New York State WIC evaluation study

Since 1972, the Special Supplemental Food Program for Women, Infants and Children (WIC) has provided supplemental foods and nutrition education to expectant and lactating women as well as infants and young children who are at nutritional risk. WIC is the nation's largest public health nutrition program. Eligibility for the program is based on identifiable nutritional risk and low income.

The WIC program serves an estimated 360,000 women, infants and children in New York State, which is one of 13 states currently supplementing federal spending with state funds. In 1989, New York State contributed \$42 million and the federal government supplied \$161 million in support of WIC program activities.

The overall goal of the WIC program is to ensure adequate nutrition during the dynamic growth stages (fetal and early childhood periods) for high-risk individuals. Prenatal supplementation aims to improve birth outcomes, specifically, low birthweight and prematurity. A recently completed New York State Department of Health study examined the association between prenatal WIC participation and birth outcomes, such as birthweight and gestational age, and the relationship between WIC participation and newborn hospital costs for Medicaid recipients.

The study was based on the linkage of WIC certification records with their corresponding Certificates of Live Birth. The WIC and vital statistics records for births outside New York City were also linked with hospital discharge data from the Statewide Planning and Research Cooperative System (SPARCS) to obtain information on each infant's first hospital stay.

Results of the Study

A comparison of the average length of stay (LOS) by payer for WIC babies versus babies whose mothers did not participate in WIC (non-WIC) revealed a significant difference in the LOS for WIC infants as compared to non-

WIC infants for Medicaid, Blue Cross/Commercial and self-pay births. Within the Medicaid study group, the average LOS was compared for selected sociodemographic variables, between WIC and non-WIC infants (Table I). The greatest differences were found for unmarried women, women with less than 12 years of education, black women and 15-19-year-old women.

The actual savings in hospital costs realized by WIC infants compared to non-WIC infants in 1988 was estimated to be \$3,680,787. The additional savings that can be realized if all non-WIC pregnant Medicaid recipients were enrolled in WIC is calculated at \$2,804,495.

The difference, then, in Medicaid hospital costs if all pregnant Medicaid recipients in upstate New York were enrolled in WIC versus not in WIC is \$6,485,282.

In an analysis of Medicaid costs, the Department of Health study found that every dollar spent on the WIC program saved at least twice that amount (\$2.35) in potential Medicaid hospital costs for newborns born to mothers who participated in WIC prenatally. This portion of the study focused on children born outside New York City, and provides a conservative statewide percentage savings estimate because New York City hospital costs are significantly higher.

Researchers estimate that the WIC program saved the lives of 160 low birthweight newborns born to women on Medicaid in 1988, and could have saved the lives of another 214 low birthweight babies if their mothers had been getting WIC services (Table II).

The infant deaths averted were due to the ability of WIC services to markedly reduce the incidence of low birthweight babies, the prime factor in infant mortality. The study found that in the 1988 study year, women on Medicaid who were not enrolled in WIC were almost three times as likely to have a very low birthweight baby (less than 2,000 grams) as women on Medicaid who were receiving the added healthy food, nutritional counseling and health care referrals that WIC provides.

In conclusion, the study showed significantly improved birth outcomes for all groups of women, Medicaid, private

TABLE I. Comparison of Average Length of Stay for Medicaid WIC and Non-WIC by Maternal Education, Marital Status, Age and Race

	Average Length of Stay (in Days)			<i>p</i> value
	WIC	Non-WIC	Difference	
Marital Status				
Not Married	3.50	4.42	-0.92	<i>p</i> <.0001
Married	3.23	3.52	-0.29	<i>p</i> <.0001
Maternal Education				
<12 yrs	3.34	4.14	-0.80	<i>p</i> <.0001
12+ yrs	3.39	3.60	-0.21	<i>p</i> <.0001
Race				
White	3.13	3.51	-0.38	<i>p</i> <.0001
Black	3.89	5.07	-1.18	<i>p</i> <.0001
Hispanic	3.51	3.92	-0.41	<i>p</i> <.0007
Other	3.75	3.65	+0.10	NS
Age				
15-19	3.33	5.30	-1.97	<i>p</i> <.0005
20-29	3.40	4.36	-0.96	<i>p</i> <.0001
30-39	4.12	4.92	-0.80	NS
40-49	3.88	4.10	-0.22	NS

TABLE II. Estimated Annual Medicaid Low Birthweight Births and Infant Deaths Averted through WIC Participation

WIC Status	Estimated Annual Number	
	Low Birthweight Births	Infant Deaths
WIC not available	9,473	1,065
Current status	7,616	905
All WIC	5,127	691

Note: Current status data based on 17,738 WIC births and 23,808 non-WIC births in 1988.

insurance and self-pay, who participated in the WIC program. These findings are supported by national studies, which have also described improved birth outcomes for WIC-enrolled women and proportionate savings similar to the New York State study.

For further information on the WIC evaluation study and for single copies of the report *The New York State WIC Evaluation: The Association Between Prenatal WIC Participation and Birth Outcomes*, contact: New York State Department of Health, Bureau of Nutrition, 844 Corning Tower, Empire State Plaza Albany, NY 12237, (518) 473-8286.

Comfort A Brother

No need for Fortune
to share a child's smile
to touch a friend's heart
to tenderly love
No need for Fame
to comfort a brother
to feel a cool breeze.
Stand tall in the sun.
Fools plan tomorrow
from yesterday's beauty.
Today is forever.

Dilemma

To right the wrongs of Nature
is God's work
so we are Gods
Or his hands
Or his brain.
And when we fail we are men
Frail, confused, hurt men.
But tomorrow we are Gods again
weaving our way
through miracles that make Life
And probe and ponder
And look through the secrets of God
To raise a fallen body
To clear a clouded mind.
And so to men we are Gods
To God we are men
And to us we are neither.
Not so, we are doctors.

Brain, Heart, Soul

Thoughts, feelings, dreams, words
fly in a frenzy
in our brains, our hearts, our very souls
and flow to my pen that I fear is false.
Would that my pen were a magic wand
or my hand were led by God
to give brain and heart and soul
the power to find truth and strength.
To give courage and heal wounds.
To truly love and be loved.
To know that pain and fear
are paths to comfort and peace.
To see a sparrow as noble as an eagle
and an eagle as gentle as a sparrow.

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**BONE MARROW TRANSPLANTATION
IN CHILDREN**

Edited by F. Leonard Johnson, MD, and
Carl Pochedly, MD. 529 pp, illustrated.
New York, Raven Press, 1990. \$125.00
(hardcover)

This is the first book which specifically focuses on pediatric bone marrow transplantation. The editors have brought together outstanding authorities in the different fields of bone marrow transplantation and together they have produced a unique book. It will be very useful for practicing pediatric oncologists, radiation therapists, hematologists, immunologists, and professionals with interest in storage diseases.

The first eight chapters essentially have a general theme beginning with the fascinating and succinct history of bone marrow transplantation written by Dr Robert A. Good. This is followed by a discussion of histocompatibility, and a detailed review of the technical aspects of bone marrow transplantation. The next two chapters present a detailed summary of immunological and hematological recovery. A discussion of the pathology of toxicity of drugs before and after the transplantation is then presented. The following six chapters discuss the indications for bone marrow transplantation. These include hematological, oncological, and other disorders. These chapters present a great deal of detail. However, the chapter on leukemia is shorter than those covering many of the rare diseases where bone marrow transplantation is not done very frequently. These six chapters provide useful guidance to pediatric oncologists in recommending bone marrow transplantation to patients. The next two chapters on the unrelated donor and partially matched donor illustrate the paucity of data in this field.

The next seven chapters summarize complications, but there is some redundancy concerning the coverage of pathology in these and the first eight chapters. However, some of this overlap is very useful. The late effects of bone marrow transplantation are then covered.

The next two chapters are very pertinent, except one might have liked more detail about out-of-pocket expenses for parents. One issue that is not addressed is the difficulty encountered by patients

and parents when they must go to new centers which have a different philosophy and different care takers. The last chapter is challenging, exciting, and focuses on the heart of the matter: bone marrow transplantation as a means to an end and not an end in itself.

The quality of each chapter is different as it is written by a different group of authors. This, however, has not interfered with the accuracy and clarity of the content of the book. There is some contradiction about management of infectious complications, but all in all it is helpful to have different views. In the absence of other comprehensive books on pediatric bone marrow transplantation, comparisons are not possible. The editors' objectives have been achieved, and this book will be helpful for many groups of people who are directly or indirectly involved in pediatric bone marrow transplantation.

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**FREUD AND MOSES: THE LONG
JOURNEY HOME**

By Emanuel Rice, MD. 266 pp. Albany,
NY, State University of New York
Press, 1990. \$49.50 (hardcover)

Freud and Moses: The Long Journey Home presents an insightful, penetrating, and brilliant alternative view of Sigmund Freud (1856-1939), one markedly different from that of Peter Gay's *A Godless Jew: Freud, Atheism and The Making of Psychoanalysis* or Ernest Jones' *The Life and Work of Sigmund Freud*.

Dr Emanuel Rice, a practicing psychiatrist and professor of psychiatry at the Mount Sinai School of Medicine of the City University of New York, has carefully examined almost all of Freud's writings and correspondence, including anecdotal and previously unpublished information. The only material that he does not examine is the correspondence between Sabina Spielrein, Jung, and Freud; those writings, discovered in 1977, in fact provide additional support for Rice's thesis. Rice maintains that there is a dichotomy between Freud's public disassociation from God, religion, and ritual and his internal religious conflicts. According

to Rice, Freud resolved this dualism by his "long journey home," determining that his life's work had indeed been concerned with the essence of Judaism, the unconscious and all of its manifestations. Rice succeeds in providing new perspectives on the life of Sigmund Freud and the relationship between psychoanalysis and religion in general, and psychoanalysis and Judaism in particular.

In the preface to the Hebrew edition of his *Totem and Taboo* (1930), Freud, referring to himself in the third person, wrote: "If the question were put to him: 'Since you have abandoned all these common characteristics of your countrymen, what is there left to you that is Jewish?' he would reply: 'A great deal, and probably its very essence.'"

It was during Freud's adolescence that he demonstrated rebelliousness toward his Jewish identity as he changed his name from Shlomo Sigismund Freud to Sigmund Freud. Nevertheless, this adolescent phase eventually gave way to a more positive Jewish identity. Freud became a member of B'nai Brith (1897), acquired a complete set of the Talmud, in both the original language and translation, and was appointed to the Board of Governors of the Hebrew University in Jerusalem (1925), demonstrating his Zionist tendencies.

Contrary to the popular view of Freud's parents as assimilated Jews, Rice effectively argues that both came from Orthodox Jewish families and continued to uphold many traditions. For example, date notations made by Sigmund's father, Jacob (1815-1896), in the family Bible indicate that he did not want to recognize the Christian calendar, in accordance with a custom prevalent among Orthodox Jews. Furthermore, Jacob's granddaughter, Judith Bernays Heller, stated that toward the end of Jacob's life, he still studied the Talmud and recited many parts of the Passover Seder by heart. Similarly, Rice presents evidence to suggest that the marriage of Jacob Freud to his bride, Amalia, was solemnized by an Orthodox rabbi.

Based on visitors' recollections that Amalia spoke only Yiddish, Rice concludes that Yiddish must have been Freud's first language, though he maintained that he was ignorant of that language and of Hebrew. Rice further contends that Freud must have received a Hebrew education as part of his stan-

dard Gymnasium curriculum. Jacob Freud placed a Hebrew inscription in the family Bible on the occasion of Sig-mund's 35th birthday, and Rice ana-lyzes it in detail, postulating that a fa-ther would not have written an indecipherable message to his son.

In addition to the family Bible, an eight-volume Philippon Bible (1858 edition) was recently discovered in Freud's library. It bore the stamp of "Rabbiner Dr Altmann" and handwrit-ten notes. How the work came into Freud's possession is not clear. What is certain, however, is that the work was previously owned by Rabbi Dr Adolf (Avraham) Altmann (*Encyclopaedia Judaica Year Book*, 1983-1985), an eminent scholar and historian, who served as rabbi in Salzburg from 1907 to 1915 and subsequently became Chief Rabbi of Trier, Germany. His sole sur-viving son, Dr Manfred Altman of Lon-don, confirms that both the stamp and the handwritten notes in question are definitely those of his father.

Freud's denial of Jewish linguistic and religious knowledge is but one indi-cation of his strong inner conflict about his Jewish identity. Publicly, he had no synagogue affiliation, nor did he prac-tice any religious ritual. On the con-trary, he was an avowed atheist, who wrote to Oskar Pfister: "Quite by the way, why did none of the devout create psychoanalysis? Why did one have to wait for a completely godless Jew?"

Yet Freud spent his life interpreting dreams, a divinely inspired activity (Genesis 40:8), and alleviating the pain of his neurotic patients. By contrast, many of his contemporaries were verbal theists who constantly were changing the meaning of their gods based on philosophical concepts of the day, all the while never interpreting dreams nor trying to understand or advance the hu-man condition. In such instances, who really believes in the essence of reli-gion—the professed atheist or the ver-bal theist?

Rice blames Freud's seeming rebel-lion against his Jewish origins on two primary interrelated factors. The first is the fact that the Freuds were outsid-ers, Austro-Hungarians (Ostjuden), among the Viennese middle class. The intense prejudice against these Jews had a profound effect on the self-esteem of these immigrants and their descen-dants. Freud attempted to eliminate any aspect of his family history that demonstrated its Eastern European ori-gins. He created a "family romance," stating (in *An Autobiographical*

Study): "I have reason to believe that my father's family were settled for a long time on the Rhine (at Cologne) . . ." We must move beyond an image that the Freud family itself helped to construct. Second, Freud had ambiva-lent feelings toward his father, Jacob, who had caused him to be an outsider. He felt the death of his father very pas-sionately. Rice sees in this relationship the classic Oedipal father-son conflict, not exclusively in sexual terms, but also in terms of power and authority. Both of these factors could account for the discrepancies between the public perso-na of Freud and his private, inner self.

The Biblical figure of Moses fasci-nated Freud for almost his entire life. His *Moses and Monotheism* represent-ed a continuation and ultimately the culmination of his quest for personal identity. In his attempt to write a biog-raphy of the Jewish people, Freud suc-ceeded in writing a true autobiography. It is interesting to note that the original title of *Moses and Monotheism* was *The Man Moses: A Historical Novel*. It is possible that the only way Freud, in his old age, could have allowed himself to come to terms with the Judaism of his father was by acting out his own Oe-dipal complex. In *Moses and Monothe-ism*, he created a de-Judaized, Egyp-tian Moses-father, had him murdered by Jews and then created a new, Jewish Moses, with whom he identified.

Freud's extreme identification with Moses led him to appoint Carl Gustav Jung as his "Joshua." He hoped to pass on the leadership of the psychoanalytic movement to a Christian and thereby save it from what he feared would be an irradicable Jewish imprint. Freud wanted psychoanalysis to become a tru-ly universal movement and certainly did not want it to remain a "Jewish science."

Freud's perception (expressed in his preface to the Hebrew edition of *Totem and Taboo*) that he fulfilled the essence of Judaism shows his understanding of the similarity between psychoanalysis and religion. Psychoanalysis ultimately refers to the analysis of the psyche, the essence of the soul and the unconscious. The exploration of the unconscious is an essential aspect of a religious life. Religion is ultimately about the rela-tionship of each individual to humanity and God. While discarding many of his family religious traditions, Freud fo-cused on the essence of the soul and its manifestations.

I would like history to view Freud as saying, "I am Joseph (your brother, the

interpreter of dreams); is my father (Moses) still alive? (Genesis 45:3).

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SYSTEMATIC TREATMENT SELECTION: TOWARD TARGETED THERAPEUTIC INTERVENTIONS

By Larry E. Beutler, PhD, and John F. Clarkin, PhD. 384 pp, illustrated. New York, Brunner/Mazel Publishers, 1990. \$40.00 (hardcover)

The late Lewis Mumford once wrote that when we try to understand things by looking at their component parts, that's science. In contrast, when we try to look at the whole, that's art. It can generally be said that books on psycho-therapy, except those that empirically study the effects or process of psycho-therapeutic interventions, are rarely written as if by scientists. More often, they either artfully extend elegant theo-ries of psychological change or argue for the superiority of one clinical ap-proach, usually based on the canoniza-tion of a single aspect of a complex phe-nomenon, over another. These common forms stand in contrast to the growing ambition in the fields of psychiatry, psychology, and psychotherapy re-search to develop an eclectic, integra-tive science of psychological treat-ments. *Systematic Treatment Selection: Toward Targeted Thera-peutic Interventions* ably addresses this challenge.

Authored by two well-respected psy-chotherapy researchers-practitioners, Larry E. Beutler, PhD, and John F. Clarkin, PhD, this volume has the orga-nization and clarity that an architect might covet. The format of the book is orderly and precise, and it is divided into major sections that examine what the authors believe to be principal fac-tors in devising individualized psycho-social interventions. They first intro-duce the reader to the foundations of eclectic psychotherapy and treatment selection and then review their prescrip-tive decision-making framework that accounts for: patient predisposing vari-ables (diagnostic conditions, patient personal characteristics, environments, and circumstances); treatment contexts (treatment setting, mode and format, frequency, and duration); relationship variables (compatibility, therapeutic alliance); strategies and techniques (se-

lecting targets for change, level of intervention, conducting therapeutic work); and training directions. Beutler and Clarkin offer a research-based model that simultaneously considers patient characteristics, their social environments, treatment settings, therapist characteristics, and a broad spectrum of available therapies. And here is where the whole becomes more than the sum of its parts.

If the field of psychiatry, and psychotherapy in particular, has been historically characterized by representatives of different theoretical commitments clamoring to be heard, these authors convey a refreshing approach. In their well-researched review of central dimensions of psychosocial treatments, they demonstrate an even-handed respect for the integrity of each aspect as it relates to other important components of assessment and intervention. Beutler and Clarkin are dedicated to differential therapeutics in their most universal rather than most parochial terms. Although the authors do assign priorities in identifying what they consider to be generic factors in psychological treatments, their choices are thoughtful and do not reflect a distinct bias in the direction of any particular theoretical approach. It is as if in their view, the entire literature on psychotherapeutic practice is theirs (and ours) for the reading and taking, not just a selected portion.

What is unique about this book is that it is research-based without being endlessly encyclopedic. The authors are reasoned and selective. Their writing is cogent, the presentation of the wide-ranging material is excellent, and their commitment to complexity rather than a single-pitch approach will frustrate readers who want a simple how-to-do-it. For this reason, *Systematic Treatment Selection: Toward Targeted Therapeutic Interventions* is not a book for casual readers or novice clinicians, despite the claims on the jacket cover. As a resource for psychotherapy researchers, Beutler and Clarkin's volume offers something unlike anything presently available. In addition, those who are in the position of training residents to think in a more sophisticated way about clinical decision-making may find it invaluable. Rather than inducting readers into a particular aesthetic or theoretical position that accords special status to certain dimensions at the expense of others, it models a more flexible position that explicitly addresses the multiple factors

influencing assessment and treatment decisions that are frequently obscured, ignored, or overlooked in the clinical context.

In sum, the scientific footing of this book is solid. This is a data-based rather than theory-driven, volume written by intelligent authors who subscribe to the notion that clinical decisions should be made on the basis of what is most likely to benefit a particular patient with a particular set of problems in a particular social context at a particular point in time. Beutler and Clarkin advocate a politics of inclusion instead of one that elevates a single psychotherapeutic truth above all others. In doing so, they recognize and value the parts as well as the whole. Although their book may lack the expressive and evocative elements that frequently characterize works in this field, they have produced one that is artfully crafted, carefully balanced, and accomplished in its precision.

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ENDOCRINOLOGY OF THERMAL TRAUMA: PATHOPHYSIOLOGIC MECHANISMS AND CLINICAL INTERPRETATION

Edited by Rajko Dolecek, MD, Lore-dana Brizio-Molteni, MD, Agostino Molteni, MD, and Daniel Traber, PhD. 469 pp, illustrated. Malvern, Pa, Lea & Febiger, 1990. \$78.50 (hardcover)

Although remarkable progress in understanding thermal trauma has been made in the past few decades, our understanding of the mechanism regulating homeostasis following thermal injury is only in its infancy. This book is intended for those who are interested in the problems of trauma in general and burn injury in particular. They will find in it many interesting observations and correlations, which will open new avenues for understanding the pathophysiology of burn injury and improving treatment possibilities. Because much of the audience with an interest in burns or critical illness are not endocrinologists, relevant endocrine concepts are reviewed in some of the chapters. Because all the observations are not yet explainable, some theoretical ideas to bring the findings together are mentioned. Some new types of treatment

are discussed as well, regardless of the fact that they may still be controversial.

Endocrine findings are rapidly accumulating and may bear on basic mechanisms in the events after burn trauma. For endocrinologists, burn injury represents a fast growing area in which interesting applications of their specialty are not yet part of formal medical training. The pathophysiologic processes after burn injury represent to some extent those that characterize critical illness in general. Thus, the findings in burn injury may be relevant to surgeons, internists, pediatricians, and others.

Throughout this book, burn trauma is regarded as a model of severe illness. The clinical effects of burn trauma are considered in relation not only to the more classic hormonal axes, but also in relation to other systems, such as the arachidonate-derived peptide cytokine, and other mediators in tissues and the endocrine response of the lungs. This book should be useful to physicians and nurses in burn centers, traumatologists, surgeons, internists, pediatricians, endocrinologists, immunologists, pathologists, and physiologists. It is not a manual for patient care, but is a resource of information about changes in an integrated physiologic system whose role in thermal injury is beginning to be appreciated on a wide scale.

The studies of the various authors are reviewed as well as those of others. It is colored by the experiences and points of view of the authors, who represent widely different backgrounds in training and geography. This permits different perspectives on common issues in the various chapters by the authors. The resulting differences in emphasis and direction among the authors allow the reader to assess these lines of thinking.

This book appears to be well organized with a focus on the various endocrine aspects which relate to death, mechanisms of pain and pain management, review of specific endocrine and hormonal relationships, review of arachidonic acid metabolites in thermal trauma, and an overall review of burn trauma as a model of severe illness. A chapter is devoted to the endocrine responses in children with thermal trauma. Chapter 16, which addresses the pathologic changes after thermal trauma, has many pictures and photomicrographs. Although these are interesting to review, they are not always helpful and not easily understood. The final chapter (18) reviews the therapeutic implications of all previously presented

materials. However, the author stresses that these data are from his own experience and burn center, so one must be cautious about transplanting these concepts to other treatment areas.

This book is unique, because it brings together the area of endocrinology research and the clinical applications of thermal trauma. While one can find individual published articles about a specific endocrinologic problem, nowhere are these brought together as in this text. This book will serve as an excellent current reference manual as well as for the future. This text should serve as a stimulus to further research in this area. It is an excellent addition to the current medical literature.

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PEDIATRIC DERMATOLOGY AND DERMATOPATHOLOGY: A TEXT AND ATLAS

By Ruggero Caputo, MD, A. Bernard Ackerman, MD, and Evita Q. Sison-Torre, MD. 391 pp, illustrated. Philadelphia, Pa, Lea & Febiger, 1990. \$150.00 (hardcover)

This book is a major transatlantic collaboration among three authors: renowned dermatologist Ruggero Caputo, director of the First Dermatology Clinic, University of Milan, Italy; A. Bernard Ackerman, director of Dermatopathology at New York University Medical Center; and Evita Q. Sison-Torre, fellow in Dermatopathology at New York University Medical Center.

This volume is divided into 30 chapters, each one dealing with a specific skin disease seen in children. They are arranged in alphabetical order, from A to C, starting with acanthosis nigricans and ending with cutis marmorata telangiectatica congenita. I infer that diseases from D to Z would be the subject of a future volume(s). The majority of the diseases are rare.

Each disease is extensively and comprehensively discussed including clinical findings (age of onset, incidence, associations, complications), clinical differential diagnosis, laboratory findings, histopathologic findings, histopathologic differential diagnosis, etiology, pathogenesis, management, course and prognosis. Short comments are added from which readers can glean many "pearls." Also included are the

criteria essential for clinical and histopathologic diagnosis. Overall, the text is excellent and richly referenced.

The authors, each with their own personal style, succeeded in "portraying the lives of lesions for each disease, rather than simply capturing a single static moment on its course, thus representing each disease as a moving picture rather than a still life."

The most remarkable section of each chapter is the color photographs of both the clinical and histopathologic features of the disease. The photomicrographs are in three magnifications: scanning, higher, and highest magnification. All the photographs without exception are extraordinarily beautiful. There are three diseases without photomicrographs: angioma serpiginosum, anhidrotic ectodermal dysplasia, and aplasia cutis congenita. Another very minor flaw is the misdirected right/left orientation of some photographs.

My favorite chapters are those on acquired melanocytic nevi and congenital melanocytic nevi. They are simply magnificent. A reader can never find in any other textbook such a thorough and explicit discussion of these two disorders. This book and its sister volume(s) are invaluable to all pediatric dermatologists, dermatopathologists, and general dermatologists who see children in their practice.

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NEUROLOGIC EMERGENCIES: RECOGNITION AND MANAGEMENT

Second Edition. Edited by Michael Salcman, MD. 462 pp, illustrated, New York, Raven Press, 1990. \$80.00 (hardcover)

This book represents an excellent introduction to the diagnosis and management of neurologic emergencies, Dr Salcman's personal style of writing is delightful, in the true Cushing tradition, so that the reader must constantly refresh his or her recollection that this is, indeed, a technical work of the highest order.

The stated goal of this work, to produce a practical volume of modest proportions that can be useful to emergency room physicians, internists, and pediatricians has indeed been achieved. There are a few workers in the field of

neuro-traumatology who bring to bear the combined research and clinical experiences that Dr Salcman, the editor, does. The work deals with the general areas of stroke and tumor, trauma, and medical and pediatric emergencies.

The general consideration section contains a superb review of cardio-respiratory physiology. The section on the medical and surgical management of stroke excels in a clear exposition of critical and practical recommendations for the management of acute stroke patients, all of which may not be obvious to medical workers outside of the neurological subspecialties. Critical data regarding prognosis as a function of diameter and volume of ganglionic hemorrhages provide a clear guide in the emergency suite. Stereotaxic and endoscopic evacuation of ganglionic hemorrhages is considered. The subtle findings, but with potential for a most hazardous outcome in cerebellar hemorrhage, are highlighted.

The chapter on neoplastic emergencies, written by the editor, excels not only by its current and comprehensive approach, but also by the clarity and ease of presentation. Critical concepts, again not universally put into practice by non-neurological medical workers, are noted, such as the risk of a lumbar puncture caudal to a partial spinal block from a metastatic malignancy.

Neurologic Emergencies is excellent in its presentation of acute head injuries. The epidemiology, diagnosis, pathophysiology and management are dealt with in a comprehensive and current fashion. Illustrations, including multiple cranial CT scans, are excellent. The formulation and utility for Glasgow Coma and Outcome Scales are reviewed. Associated medical problems and their managements are also reviewed in a succinct and highly useful manner.

The diagnosis and management of spinal injuries are presented in a clear, systematic and useful way with critical areas being emphasized, such as 4% to 20% of patients with severe cranial injury having associated cervical spine injuries. A practical synopsis of spinal cord syndromes, root innervation, and summary of scale for documenting motor strength are clearly and succinctly presented. The comprehensive chapter on acute nerve root compression, provided by the editor, includes the experiences of a seasoned clinician who has been there many times, in combination with profound knowledge of the anatomy and physiology, as well as historical

considerations. The area of peripheral nerve injury and its management is clear and brief, but comprehensive, providing details of neuroanatomy, pathophysiology, as well as management. The section on medical emergencies matches that of its preceding neurosurgical sections. The use of neuroradiology in the evaluation of the patients with seizures is exemplary. Acute polyneuropathies are reviewed from the viewpoint of epidemiology, clinical presentation, pathology, as well as management. Acute respiratory muscular failure, associated with infectious as well as metabolic derangements, is also reviewed from the viewpoint of anatomy and physiology, clinical features and diagnostic work-up, as well as therapy. The diagnosis and management of bacterial meningitis and viral encephalitis is also dealt with in a succinct, but systematic and comprehensive fashion. Toxic and metabolic encephalopathies are reviewed in terms of diagnosis and management, including a consideration of benzodiazepines, opiates, cocaine, and phencyclidine (angel dust), organo-phosphorus compounds, and non-barbiturate hypnotics. Encephalopathy and vitamin deficiency, hepatic encephalopathy, endocrine encephalopathy, as well as the altered mental status of AIDS are also consid-

ered. Pediatric neurologic emergencies are reviewed, giving special emphasis to the history and the physical examination in children, as well as to pediatric illnesses, such as febrile seizures, infantile spasms and Reye's syndrome.

The final chapter in the book deals with pediatric neuro-surgical emergencies, trauma, traumatic lepto-meningeal cyst, spinal cord injuries, seizures, hydrocephalus, cranio-spinal dysraphic syndromes, encephaloceles, and child abuse in a brief but useful, current, and comprehensive manner.

All chapters are amply referenced to the literature.

It is not feasible for the editor of any textbook, due to the time between writing and publication, to have every contributor's section totally current with ongoing practice. Not surprisingly, a few areas have not been well covered. These include the current role of MRI in both the diagnosis of acute brain ischemia (patho-physiology section), as well as in acute root compression, and the results of the Cooperative Study with regard to STA-MCA and carotid endarterectomy.

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HANDBOOK OF VERTIGO

By Michael E. Glasscock III, MD, Roberto A. Cueva, MD, and Britt A. The-dinger, MD. 122 pp, illustrated. New York, Raven Press, 1990. \$49.00 (hard-cover)

The theme of the book is an elementary overview of a labyrinthine or vestibular system complaint. The subjects are handled in a very simple, general manner. The preface by the senior author, Dr Glasscock, alludes to the general review of anatomy and physiology, vestibular disorders, diagnostic assessments and case histories in an abbreviated approach. For the non-otorhinolaryngologist this short, 122-page text is a valuable source of anatomy, physiology, and diagnostic considerations. I regret that simple medical and/or surgical management is not further explored.

The authors present the material in an organized, concise, and easily digestible fashion. I know of no similar elementary labyrinthine system treatise and this text would be a welcomed additive to the general medical library.

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Two warnings for women

Two recent papers in the *American Journal of Epidemiology* warn women that smoking may increase their risk of tubal pregnancy, and that frequent douching may increase their risk of cervical carcinoma.

In the first report, Stergachis et al (1991; 133:332-337) interviewed 274 women aged 18 years or older who had been treated in the hospital for tubal pregnancy between October 1981 and September 1986. Interviews with 727 control subjects—all women of childbearing age—completed the study group. The authors demonstrated an increased relative risk of tubal pregnancy of 1.4, "largely restricted to women who smoked at the time of conception and to those who had stopped smoking less than 2 years prior to that time." There was no apparent association with the amount smoked, the duration of smoking, or the age started.

There is evidence to suggest that exposure to nicotine delays entry of the ovum into the uterus—believed to be the mechanism behind tubal pregnancy—by reducing tubal motility and impairing the propelling action of cilia in the fallopian tubes.

Unexpectedly, the authors found that in heavy smokers, the risk of tubal pregnancy declined. They attribute this to the fact that heavy smoking suppresses ovulation and would thereby limit the opportunity for ectopic implantation.

In another study, Gardner et al (1991; 133:368-375) determined that frequent vaginal douching increases a woman's risk of in situ and invasive cervical carcinoma. The women in this case-control study reported having douched primarily for reasons of cleanliness and hygiene.

Women who douched more than four times per month (or more than once a week) seemed to be at greater risk for cervical carcinoma (odds ratio = 4.7). Variations in the type of douche used (water, water and vinegar, or commercial preparations) had little effect on this four-fold differential in cancer risk.

Although any douching would alter the vaginal environment, by changing the pH or diluting the vaginal secretions, more frequent douching would sustain these effects, perhaps causing a change in the vaginal flora and increasing the susceptibility to pathologic factors. "The strongest effect was seen in those who used water/vinegar preparations, which suggests that pH changes might be important."

Prevalence of HIV infection among childbearing women in the United States

"More than three fourths of women diagnosed with AIDS are of reproductive age, and transmission of human immunodeficiency virus (HIV) from mother to infant accounts for over 80% of AIDS in children" (*JAMA* 1991; 265:1704-1708). The epidemic spread of HIV infection and AIDS includes a growing number of women and children. "To understand the scope of the HIV epi-

demic, to predict its future course, and to recognize opportunities for prevention," Gwinn et al from the Centers for Disease Control and the National Institutes of Health drew data from a nationwide survey to determine the prevalence of HIV infection in childbearing women.

To detect maternal antibodies to HIV, the authors assayed dried blood specimens collected from neonates as a routine screening procedure. For the study year, 1989, an estimated 1.5/1,000 women who gave birth in the United States were infected with HIV. With an estimated perinatal transmission rate of 30%, the number of infants born in the US in 1989 who acquired HIV in utero would be about 1 in 2,200. Further extrapolating these data, the authors state that "as many as 80,000 reproductive-age women could be currently infected with HIV."

Voluntary screening for HIV for all pregnant women, all women planning a pregnancy, and all neonates could enable appropriate counseling and follow-up care for mothers and their babies.

Alpha-interferon therapy yields long term remission of chronic hepatitis B

This study group of 64 patients was treated for chronic hepatitis B with alpha-interferon (*Ann Intern Med* 1991; 114:629-634). Prior to treatment, all of the patients had chronic elevations in serum alanine and aspartate aminotransferase activities, presence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) or hepatitis B virus (HBV) DNA, and DNA polymerase activity in serum.

Twenty-three of the 64 patients (36%) responded to the alpha-interferon treatment with a loss of HBV DNA and DNA polymerase activity, loss of serum HBeAg, and a decrease in serum aminotransferase levels. After follow-up periods of three to seven years following treatment, 20 of these 23 patients remained free of HBeAg, while three patients relapsed within one year of treatment. In comparison with a study population of 23 patients with chronic hepatitis B who spontaneously lost HBeAg and HBV DNA, loss of HBsAg was more prevalent and occurred sooner in the group treated with alpha-interferon.

FDA update

The Food and Drug Administration has approved the following medications:

Filgrastim, a genetically engineered form of human granulocyte colony-stimulating factor (G-CSF) to prevent infections associated with chemotherapy.

Succimer, an oral treatment for severe lead poisoning in children.

Idarubicin, for use in combination with other agents to treat acute myeloid leukemia in adults.

Odansetron hydrochloride, an intravenous drug to prevent nausea and vomiting that accompanies cancer chemotherapy.

Robert H. Blom, MD, Binghamton. Died March 23, 1991; age 62. Dr Blom was a 1957 graduate of the Medische Faculteit, Rijksuniversiteit te Leiden, Leiden, Netherlands. He was a Diplomate of the American Board of Family Practice. His memberships included the American Academy of Family Physicians, the American Geriatrics Society, the Broome County Medical Society, and the Medical Society of the State of New York.

Marion Joseph Chimera, MD, Palm City, Florida. Died February 24, 1991; age 84. Dr Chimera was a 1932 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a member of the International Academy of Proctology, the Steuben County Medical Society, and the Medical Society of the State of New York.

M. John Clarke, MD, Nogales, Arizona. Died March 18, 1991; age 76. Dr Clarke was a 1942 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Fellow of the American College of Surgeons. His memberships included the New York Academy of Medicine, the American College of Occupational Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Samuel Lewis Cohen, MD, Fort Lauderdale, Florida. Died October 11, 1990; age 90. Dr Cohen was a 1924 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Arminio L. Colantuono, MD, Manhasset. Died January 14, 1991; age 89. Dr Colantuono was a 1925 graduate of the New York University School of Medicine. He was a Qualified Fellow of the International College of Surgeons. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Nicholas J. Czukur, MD, Nyack. Died February 20, 1991; age 74. Dr Czukur was a 1941 graduate of the Faculte de Medecine, Universite de Lausanne,

Lausanne, Switzerland. He was a member of the Medical Society of the County of Rockland and the Medical Society of the State of New York.

Anthony M. DeBonis, MD, Troy. Died November 8, 1990; age 59. Dr DeBonis was a 1960 graduate of the Facolta di Medicina e Chirurgia, Universita di Bologna, Bologna, Italy. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Chest Physicians. He was a member of the American Thoracic Society, the Medical Society of the County of Rensselaer, and the Medical Society of the State of New York.

Francis E. Ehret, MD, Kenmore. Died February 23, 1991; age 79. Dr Ehret was a 1937 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. His memberships included the New York Academy of Medicine, the American Academy of Allergy, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Rocco Anthony Farano, MD, Troy. Died January 20, 1991; age 63. Dr Farano was a 1956 graduate of Georgetown University School of Medicine, Washington, DC. He was a Diplomate of the American Board of Family Practice and a Fellow of the American Academy of Family Physicians. His memberships included the Pan American Medical Association, the American Public Health Association, the American Geriatrics Society, the Medical Society of the County of Rensselaer, and the Medical Society of the State of New York.

Grant Tracy Fisher, MD, Clearwater, Florida. Died March 7, 1991; age 90. Dr Fisher was a 1925 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Fellow of the American College of Surgeons. He was a member of the New York Academy of Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Armand Hammer, MD, Los Angeles, California. Died December 10, 1990; age 93. Dr Hammer was a 1921 graduate of Columbia University College of

Physicians and Surgeons. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Charles Francis Hawley, MD, Binghamton. Died March 23, 1991; age 90. Dr Hawley was a 1932 graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania. His memberships included the New York Academy of Medicine, the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, Inc, the Broome County Medical Society, and the Medical Society of the State of New York.

John Henry P. Holden, MD, Chatham, Massachusetts. Died February 20, 1991; age 67. Dr Holden was a 1948 graduate of Albany Medical College. He was a Diplomate of the American Board of Surgery and a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Albany and the Medical Society of the State of New York.

George Adelbert Keating, MD, Purchase. Died February 20, 1991; age 80. Dr Keating was a 1938 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Diplomate of the American Board of Anesthesiology and a Fellow of the American College of Anesthesiologists. His memberships included the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, Inc, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Michael Bernard Klein, MD, Lowville. Died December 1, 1990; age 49. Dr Klein was a 1974 graduate of the Universite Libre de Bruxelles, Faculte de Medecine et de Pharmacie, Brussels, Belgium. He was a Diplomate of the American Board of Psychiatry and Neurology. He was a member of the American Psychiatric Association, the Medical Society of the County of Lewis, and the Medical Society of the State of New York.

Anthony M. LaSala, MD, Garden City. Died March 19, 1991; age 78. Dr LaSala was a 1939 graduate of New York Medical College. He was a Diplomate

of the American Board of Otolaryngology. He was a member of the American Academy of Ophthalmology and Otolaryngology, the Nassau County Medical Society, and the Medical Society of the State of New York.

Erich R. Mamlok, MD, Vestal. Died March 20, 1991; age 77. Dr Mamlok was a 1939 graduate of the Medizinische Fakultät, Universität Basel, Basel, Switzerland. He was a Diplomate of the American Board of Psychiatry and Neurology and a Fellow of the American College of Chest Physicians. He was a member of the American Psychiatric Association, the Broome County Medical Society, and the Medical Society of the State of New York.

Stanley Moe Mark, MD, Whitestone. Died March 18, 1991; age 81. Dr Mark was a 1933 graduate of New York University School of Medicine. He was a Fellow of the American College of Allergists and a Fellow of the American Academy of Family Physicians. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Reuben R. Meyers, MD, Williamsville. Died February 25, 1991; age 80. Dr Meyers was a 1934 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a member of the Medical Society of the County of Erie and the Medical Society of the State of New York.

Salvator Militello, MD, Williamsville. Died February 24, 1991; age 75. Dr Militello was a 1940 graduate of St Louis University School of Medicine, St Louis, Missouri. He was a member of the New York Academy of Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Maria E. Mintz, MD, Glens Falls. Died November 28, 1990; age 80. Dr Mintz was a 1935 graduate of the Medizinische Fakultät, Universität Basel, Basel, Switzerland. She was a member of the Medical Society of the County of Warren and the Medical Society of the State of New York.

Stanley Lawrence Neiman, MD, Brooklyn. Died December 1, 1990; age 55. Dr Neiman was a 1959 graduate of the University of Toronto, Faculty of Medicine, Toronto, Ontario, Canada.

He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. He was a member of the American Public Health Association, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

George Francis Nevin, MD, Cortland. Died February 3, 1991; age 73. Dr Nevin was a 1943 graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio. He was a member of the Cortland County Medical Society and the Medical Society of the State of New York.

Charles K. Osgood, MD, Liverpool. Died March 4, 1991; age 69. Dr Osgood was a 1946 graduate of Harvard Medical School, Boston, Massachusetts. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. His memberships included the New York State Society of Internal Medicine, the American Society of Internal Medicine, the Onondaga County Medical Society, and the Medical Society of the State of New York.

Abelardo Victor Paseiro, MD, New York. Died December 16, 1990; age 57. Dr Paseiro was a 1961 graduate of the Universidad de Buenos Aires Facultad de Medicina, Buenos Aires, Argentina. He was a Diplomate of the American Board of Physical Medicine and Rehabilitation. He was a member of the American Academy of Physical Medicine & Rehabilitation, the New York County Medical Society, and the Medical Society of the State of New York.

Louis Pelner, MD, Coconut Creek, Florida. Died November 23, 1990; age 83. Dr Pelner was a 1933 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Allergists, a Fellow of the American College of Cardiology, and a Fellow of the American College of Gastroenterology. His memberships included the Clinical Society, New York Diabetes Association, the Academy of Psychosomatic Medicine, the American Geriatrics Society, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Michel Jean-Mar Petit, MD, Ogdensburg. Died January 15, 1991; age 53.

Dr Petit was a 1962 graduate of Ecole de Medecine et de Pharmacie, Université d'Etat d'Haiti, Port Au Prince, Haiti. He was a member of the Medical Society of the County of St Lawrence and the Medical Society of the State of New York.

Jose Guadalupe Reyes, MD, Wappingers Falls. Died March 7, 1991; age 91. Dr Reyes was a 1925 graduate of Georgetown University School of Medicine, Washington, DC. He was a member of the New York State Dermatological Society, the American Academy of Dermatology, the Bronx County Medical Society, and the Medical Society of the State of New York.

Gilbert Mitchel Schiff, MD, Jamaica. Died February 26, 1991; age 62. Dr Schiff was a 1957 graduate of the Faculté de Medecine, Université de Genève, Geneva, Switzerland. He was a Diplomate of the American Board of Dermatology, Inc. His memberships included the New York State Dermatological Society, the American Academy of Dermatology, Pan American Medical Association, the American Geriatrics Society, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Mark Silberman, MD, Bayside. Died January 3, 1991; age 42. Dr Silberman was a 1975 graduate of Facultad de Medicina, Universidad Autonoma de Guadalajara, Guadalajara, Jalisco, Mexico. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Barney Sisserson, MD, Golden Beach, Florida. Died October 30, 1990; age 83. Dr Sisserson was a 1934 graduate of the New York University College of Medicine. He was a Fellow of the American College of Allergists. He was a member of the Medical Society of the County of Orange and the Medical Society of the State of New York.

Jacob L. Stein, MD, Brooklyn. Died February 3, 1991; age 97. Dr Stein was a 1918 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Pediatrics and a Fellow of the American Academy of Pediatrics. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Edward D. Stevenson, MD, Newark. Died March 6, 1991; age 85. Dr Stevenson was a 1934 graduate of Georgetown University School of Medicine, Washington, DC. He was a member of the American Psychiatric Association, the Medical Society of the County of Wayne, and the Medical Society of the State of New York.

Leopold Tabatznik, MD, New Paltz. Died June 26, 1990; age 90. Dr Tabatznik was a 1930 graduate of Friedrich-Wilhelms Universitaet Medizinische Fakultaet, Berlin, Germany. He was a member of the Bronx County Medical Society and the Medical Society of the

State of New York.

Rudolph Turnbull, MD, Bronx. Died February 8, 1991; age 66. Dr Turnbull was a 1953 graduate of Howard University College of Medicine, Washington, DC. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

James W. Walton, MD, Clearwater, Florida. Died January 27, 1991; age 87. Dr Walton was a 1928 graduate of The University of Western Ontario, Faculty of Medicine, London, Ontario, Canada. He was a member of the American Gastro-Enterological Association, the

Medical Society of the County of Orange, and the Medical Society of the State of New York.

Arthur H. Weinstein, MD, Roslyn Heights. Died March 9, 1991; age 85. Dr Weinstein was a 1932 graduate of the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. He was a Diplomate of the American Board of Family Practice and a Fellow of the American Academy of Family Physicians. He was a member of the American Society of Colon and Rectal Surgeons, the Medical Society of the County of Kings, and the Medical Society of the State of New York.



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July 20–27. Ninth Annual Medical Seminar: Topics in Contemporary Medicine. 23 Cat I Credits. Plummer's Great Slave Lake Lodge, Northwest Territories. Contact: Joseph F. Bocklage, MD, 103 Oakdale Medical Center, 3366 Oakdale Ave N, Minneapolis, MN 55422. Tel: (612) 588-9478.



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1991

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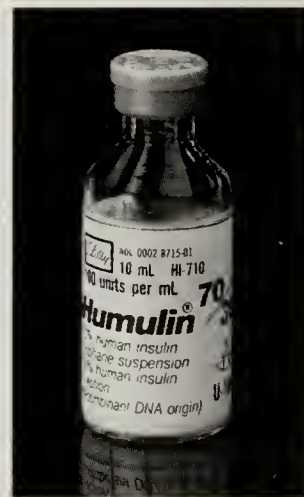
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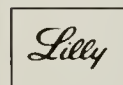
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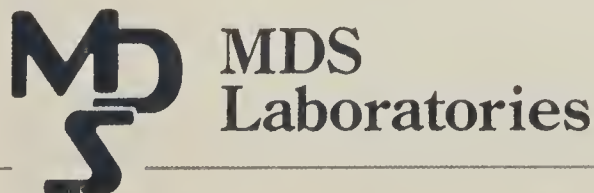
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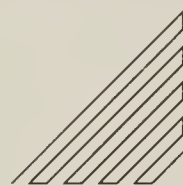
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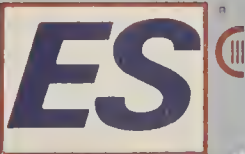
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	Constipation	Respiratory Depression	Sedation	Emesis	Physical Dependence
HYDROCODONE		X			X
XYCODONE	XX	XX	XX	XX	XX

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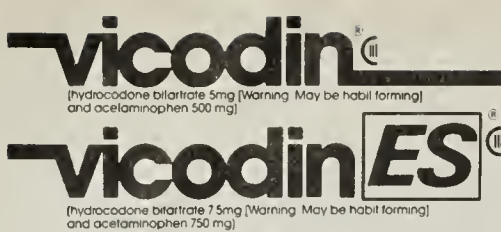
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Pneumatocelles and pneumothorax in *Pneumocystis carinii* pneumonia

Pneumatocelles are thin-walled cystic lesions in the lungs, usually occurring in association with acute pneumonia. They are characterized by a tendency to change rapidly in size and appearance. They are usually transient, although persistence for longer than two years is known.¹

Discussion of pneumatocelles is complicated by the terminology used to describe air-filled spaces in the lung, which includes synonymous and overlapping terms. This nomenclature has been codified by the Fleischner Society² as published in the *American Journal of Roentgenology*. The general term to describe circumscribed, thin-walled, gas-filled lung lucencies greater than 1 cm in diameter is cyst or air cyst. This "term is entirely nonspecific and, if possible, a more specific term (bleb, bulla, or pneumatocelle) is preferred."² Bleb and bulla are essentially synonymous terms. Pneumatocelles differ from blebs and bullae in their association with pulmonary consolidation, in their tendency to rapid change, and in their eventual resolution. Cavity and abscess should also be mentioned in a listing of gas-containing lung spaces. A cavity is an area of lucency within a zone of lung consolidation, a mass, or a nodule. An abscess is a mass within the lung parenchyma that, if it communicates with the bronchial tree, contains a cavity.²

A large number of infectious agents may result in pneumatocelle formation. The most common etiology is staphylococcal pneumonia in children, but a number of others including *Pneumocystis carinii*, *Pneumococcus*, *Klebsiella influenzae pneumoniae*, *Hemophilus*, *Escheria coli*, *Mycobacterium tuberculosis*, *Proteus mirabili*, *Pseudomonas*, group A streptococcus, viral pneumonia, and hydrocarbon-induced pneumonia have been reported.

The pathogenesis of pneumatocelle formation remains to be fully established. Two major theories have been advanced to explain their development. The first is the check-valve theory, which postulates that a pneumatocelle represents an area of localized emphysema caused by check-valve obstruction, such that the airway is open in inspiration and closed in expiration. This may result from inflammation and exudation within the airway. A variation on this posits rupture at a site of necrosis of the bronchial or bronchiolar walls with drainage from the necrosis

parenchyma, forming a cyst that enlarges due to a check-valve in the bronchial wall.

A proposed alternate mechanism is that leakage of air from the inflamed respiratory tree into the interstitial space forms a route to the subpleural space where air collection may occur. This mechanism does not exclude a check valve. It implies pulmonary interstitial emphysema (PIE), or the presence of air in the lung interstitium. This is discussed in the article by Efferen and Hendler³ in this issue of the *Journal*.

Air in the interstitium may remain localized; may dissect to produce pneumothorax, pneumomediastinum, or subcutaneous emphysema; and may even produce pneumopericardium and pneumoperitoneum. Pathologic evidence offers support for both interstitial air⁴ and necrosis mechanisms with check-valve formation⁵ in the origin of pneumatocelles. It is possible that both mechanisms are operative to a varying extent in different disease states.

The clinical course of a patient with pneumonia complicated by pneumatocelles is variable and more generally related to the extent and severity of the pneumonia, its susceptibility to treatment, and to the underlying condition of the patient, than it is to the pneumatocelles. Pneumatocelles are usually asymptomatic. They may enlarge to cause displacement and compression of the adjacent lung and mediastinum, resulting in cardiorespiratory insufficiency, which requires urgent treatment. Spontaneous pneumothorax may also occur. At times, an enlarging pneumatocelle is difficult to distinguish not only clinically, but even radiographically, from a pneumothorax. In an emergency, they may be treated as a pneumothorax with intracavitary suction through a chest tube. Alternately, thoracotomy and surgical excision may be performed.⁶

In this issue of the *Journal*,⁴ Efferen and Hendler report a case of *Pneumocystis carinii* pneumonia (PCP) in a patient with the acquired immunodeficiency syndrome (AIDS). The course of illness of their patient was complicated by pneumothorax, requiring chest tube drainage. In the pre-AIDS literature, PCP was a rare cause of pneumatocelles. Since 1987, it has become apparent that pneumatocelles often occur in the course of PCP in patients

with AIDS. De Lorenzo et al reported cystic lesions in 13 of 104 patients with PCP and AIDS.⁷ Sandhu and Goodman report pneumatoceles in 10 of 100 consecutive AIDS patients with PCP.⁸ Gurney and Bates report that 8 of 40 patients with PCP developed pneumatoceles, and 7 of the 8 had AIDS.⁹ The lesions reported by these authors follow the general course of pneumatoceles, arising in association with pneumonia, with a tendency to change in size and resolve.

The incidence of pneumatocele formation is far higher than is often realized. The host response to PCP in AIDS includes a predilection for development of these gas-filled cysts through unknown means. The mechanism of check-valve formation is thought to be necrosis, which is not a characteristic of PCP. It may be speculated that PIE is a more likely pathogenesis. This could be due to altered elastase production by neutrophils and macrophages, producing an imbalance in protease and antiprotease activity¹⁰ leading to alveolar damage and rupture of the alveolar walls, resulting in PIE. Alternately, increased elastase activity could result in areas of emphysema presenting as pneumatoceles. PCP appears to result in remodeling of lung architecture, with alveolar-interstitial pneumonitis and fibrosis.⁷ It is possible that it may also predispose to alveolar rupture and interstitial emphysema.

It is uncertain how frequently pneumothorax occurs in association with pneumatocele. Sandhu and Goodman do not report any pneumothoraces,⁸ and only one of Gurney's patients developed pneumothorax.⁹ DeLorenzo et al report 6 spontaneous pneumothoraces and 15 procedure or barotrauma related pneumothoraces in 104 patients.⁷ However, these were not necessarily related to the cystic lesions they reported. Regardless of pneumatocele, spontaneous pneumothorax is a well recognized complication of PCP in AIDS.¹¹ PIE may be a unifying explanation of both phenomena, pneumatocele and pneumothorax.

It is likely that positive pressure may play a part in the development of pneumatoceles, whether a check-valve or PIE is the mechanism of formation. Caldwell et al, when studying anesthetized rabbits, found that increased intrapulmonary pressure was the main physiologic factor, inducing interstitial emphysema,¹² probably through alveolar rupture. Likewise, if a check-valve mechanism is at work, positive pressure would be expected to lead to distention of the gas-filled space. However, many pneumato-

celes develop without positive pressure, indicating that it is not a necessary condition. Nevertheless, it is prudent for this, as well as for general medical considerations, to limit inspiratory positive pressure and positive end expiratory pressure to that amount needed to oxygenate and ventilate the patient. Ideally, peak airway should be kept below 40 cm of H₂O and certainly below 80 cm of H₂O to avoid barotrauma. Other factors, such as vigorous cough and high lung volumes, may also predispose to both pneumatocele and pneumothorax.

In summary, patients with AIDS and PCP are predisposed to pneumatoceles and pneumothorax. On occasion, an enlarging pneumatocele may produce the same effects as a tension pneumothorax. The pathogenesis of pneumatocele remains in question, with both PIE and check valves as viable theories. Perhaps pathologic data from victims of PCP will clarify this. Although the risk of pneumothorax in a patient with pneumatocele is not established, it is clear that the potential for rupture is present, and preparation for management of a potential pneumothorax should be made.

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Kaizen, the changing face of health care

There is a changing face to the dimensions of health care regulations, which deserves our close attention. The Health Care Financing Administration (HCFA) has encouraged the American Peer Review Association via its member Peer Review Organization (PRO) to embark on a program of "kaizen," the Japanese word for quality improvement.

Borrowing from the concepts of Deming¹ and Juran², which were so successfully applied to Japanese industry, the philosophy is being applied to health care. With continuous improvement one moves away from looking for

the bad physician and begins to examine failures of the system. For example, what happens once the physician has made the diagnosis and written the orders? Where are the breakdowns that plague the system and what can be done about them? If this concept is to succeed, physicians, payers, and providers must each do their part.³ Physicians should supply leadership and accountability. Hospitals will have to invest in quality improvement. Payers will have to respect physicians and work with them. The doctor-patient relationship must be strengthened. There is still some concern about the mixed signals from the regu-

latory agencies. A commitment persists to finding quality problems that have been allegedly missed and taking the appropriate actions. This seems to stress the search for bad apples rather than examining the norm. The current thrust of PROs may thus be modified to reflect these new initiatives.

What are some of the elements of this change, and how will they affect health care? Three initiatives have claimed a good deal of attention, outcomes management, uniform clinical data sets (UCDS), and small-area pattern analysis.

Outcomes management has been suggested by Ellwood⁴ as a tool to link physicians, patients, and health executives. It consists of a national data base that can relate medical intervention with health outcomes and money. Outcomes management would rely on standards, guidelines, patient well-being, and clinical and outcomes data. The results would be analyzed and disseminated. Ellwood admits that there are questions regarding patient subjectivity, the need to adjust for co-morbidity, and the controversy surrounding standards. The problems related to medical records are also acknowledged.

This is a massive endeavour that would require funding from government, private foundations, and payers. Lohr⁵ states that a difficult aspect of outcome-directed efforts will be to adjust outcomes for the risk factors present in the population studied. She asserts that process measures may be needed as proxies for outcomes of patients with complex medical conditions when the many variables that influence outcomes of care cannot be controlled. The link between process and outcomes needs to be clearly understood.

UCDS is a pilot project of HCFA.⁶ Its purpose is the development of a new mechanism, an expert system, for the screening by PROs of inpatient cases for utilization and quality of care problems. The primary objective of UCDS is to provide PROs with a standardized and objective screening mechanism in order to improve the efficiency and consistency of identifying confirmed quality and utilization problems. It would also create a powerful epidemiologic clinical data base to aid effectiveness research. This involves detailed clinical data including patient risk factors, processes of care, and outcomes on a case-by-case basis.

This is a two-part approach in which the data describe the clinical characteristics of the patient at admission, processes of care, and outcomes. The computerized, medical-finding algorithms evaluate the collected data and determine whether or not physician review is warranted to confirm a potential problem. This initiative is being tested by the Wisconsin PRO and others. The program is still in its infancy and is still being modified. The plan is for UCDS to become the basis of PRO monitoring of Medicare inpatient hospital care in the future.

Small-area analysis in which small, geographically designed areas are delineated and hospitalization rates are calculated for the area, represents a means of furnishing the data for continuous improvement.⁷ Disease-specific patterns of hospital admissions, with controls for patient age and sex, are compared with those in other geographic

areas. This approach to physicians' practice patterns is population based and not hospital or physician based. All the members of the given population are studied for variations in health care costs. This tool permits the comparison of physicians' practice patterns in small areas and is believed to be nonjudgmental. It allows for an educational rather than a punitive intervention. The ultimate aim is to avoid confrontational moves and to seek a more collaborative and harmonious partnership.

In this dimension, there appears to be an evolution from confrontation to consensus and individual responsibility. There is a convergence of forces and resources to improve the quality of care. All the stakeholders of health care will be asked to increase their involvement. Medical organizations will have prominent roles in this endeavour. We should do what we can to make sure that these improvements are done right. The ideas and the principles of quality must be agreed and implemented.

This admirable push toward improving the quality of our performance should not cause us to ignore the caveat, "Perfection is Possible, Excellence is Elusive." The scientific engineering of Deming and Juran^{1,2} applied extremely well to the industrial endeavours of the Japanese, when they sought to reduce the number of assembly line rejects. One applies this concept to health care with the understanding that patients are not nuts and bolts and that all institutions are not starting with the same resources. Municipal hospitals suffer from budget restraints and large volumes of high-risk patients with a multiplicity of social and economic problems. Rural hospitals have to deal with the burdens of a far-flung population and limited resources. Universities and affiliated hospitals carry triple responsibilities of teaching, providing patient care, and educating. Such institutions are severely hampered in their efforts to provide quality care. Awareness of these and other particulars should be kept, and the data carefully assessed. It is hoped that these initiatives will solve some of the pressing problems confronting our health care system.

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Coronary artery bypass grafting

The relationship of surgical volume, hospital location, and outcome

JONATHAN ZELEN, MD; THOMAS V. BILFINGER, MD; CONSTANTINE E. ANAGNOSTOPOULOS, MD

ABSTRACT. The relationship between mortality, surgical volume, and location was investigated in the university medical centers (UMCs) in the Greater New York metropolitan area for patients undergoing coronary artery bypass grafting (CABG) in 1986. Three high-volume and five low-volume institutions, with a total of 49 surgeons, performed a total of 3,408 CABG operations. The crude mortality rates were 4% for simple, 14.7% for complex, and 5.3% combined for all UMC CABG operations. The crude mortality rates for CABG operations in high- and low-volume centers were respectively 3.6% and 4.8% for simple and 16.1% and 11.3% for complex operations. No statistically significant differences between urban (N = 6), suburban (N = 2), high-volume (N = 3), or low-volume (N = 5) centers or physicians were found (all *p* values > 0.05). Taken together, these findings suggest that surgical volume and location are not significant factors for predicting outcome for CABG.

(NY State J Med 1991; 91:290-292)

Recent studies¹⁻⁴ have alluded to an inverse relationship between the number of times a hospital or surgeon performs a procedure and the in-hospital mortality rates for that procedure. Other studies⁵⁻⁸ have focused on preoperative patient risk stratification in order to demonstrate that the patient's preoperative severity of illness is the most important factor affecting postoperative morbidity and mortality. These studies taken together with cost analysis reviews^{9,10} represent the increased awareness and concern of hospitals, physicians, and state agencies regarding quality of patient care and fiscal responsibility. In an attempt to improve the definition of patient risk, the New York State Department of Health¹¹ (DOH) has developed its own criteria, which endorse Parsonnet et al's⁵ stratification of risk criteria for preoperative evaluation. In addition, the New York State DOH¹¹ has expressed tentative acceptance of the Hannan et al criteria,¹ which suggest an inverse relationship between surgical volume and mortality and which advocate restricting operative procedures to high-volume hospitals and surgeons. The DOH is currently undertaking an extensive analysis of this relationship throughout the entire state of New York.

Does lower surgical volume or hospital location ad-

versely affect surgical outcome? To answer this question, we performed a comparative analysis of the mortality rates for coronary artery bypass grafting (CABG) procedures in the cardiac surgical programs of university medical centers (UMCs) located in the Greater New York metropolitan area for the year 1986.

METHODS

Comparison of survival in the Greater New York UMC setting following coronary artery bypass grafting was conducted using data supplied from the statewide planning and research cooperative system maintained by the New York DOH's Bureau of Hospital Services¹² for the 1986 calendar year. A total of eight centers, six urban and two suburban, and 49 surgeons, 36 urban and 13 suburban, were included in the study. UMCs and surgeons were compared in relation to surgical volume, physician volume, hospital location, and complexity of cases according to the criteria of Hannan et al¹ (< 650 cases per hospital = low volume, > 650 cases per hospital = high volume; < 116 cases per surgeon = low volume, > 116 cases per surgeon = high volume; a complex case is defined as any case involving more than just coronary revascularization, such as CABG plus valve or CABG plus aneurysmectomy). Crude mortality data were calculated by dividing the number of reported mortalities by the total number of CABG operations. A surgically related mortality was defined as any death within 30 days of operation or death prior to hospital discharge for a given operation. Due to the small sample size, statistical significance was evaluated using Fisher's exact probability test, where a *p* value < 0.05 indicates statistical significance.

RESULTS

Of the eight centers in the study, three were identified as high-volume and five as low-volume based on the number of CABG procedures (Table 1). Of the three high-volume centers, two were located in urban areas. Thus, the study group consisted of four urban low-volume centers, two urban high-volume centers, and one high- and one low-volume suburban center. Twenty-seven percent (13/49) of the physicians were considered high volume, whereas 73% (36/49) were considered low volume. Additionally, 33% (1/3) of high-volume centers had low-volume physicians, whereas no low-volume center had high-volume physicians. A total of 3,408 CABG operations were performed in the eight study hospitals—3,014 simple and 394 complex. High-volume hospitals accounted for 45% and low-volume hospitals accounted for 55% of the total cases. High-volume physicians performed 45%, and low-volume physicians performed 55% of the total operations. The overall metropolitan mortality rates for simple and complex CABG procedures were 3.7% and 14.7%,

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TABLE I. Hospital and Physician Statistical Data for CABG Operations

Hospital	1	2	3	4	5	6	7	8	Total
Hospital volume	Low	Low	High	High	High	Low	Low	Low	—
Physician volume	Low	Low	High	Low	High	Low	Low	Low	—
No. of surgeons	7	6	6	8	7	6	6	3	49
No. of operations									
Total	175	166	713	643	806	460	204	131	3,408
Simple*	163	154	624	581	678	425	271	118	3,014
Complex*	12	12	89	62	128	45	33	13	394
Mortality rate (%)									
Combined	10.3	7.8	6.0	5.4	4.2	3.2	5.3	3.8	5.3
Simple	9.2	7.1	4.8	3.8	2.9	2.8	4.8	2.5	3.7
Complex	25.0	16.7	20.2	21.0	10.9	6.7	9.1	15.4	14.7

* Simple, CABG only; Complex, CABG plus aneurysmectomy and/or valve replacement.

respectively (see Table I for mortality rates by individual hospital). High- and low-volume centers had mortality rates of 3.6% vs 4.8% for simple and 16.1% vs 11.3% for complex CABG procedures, respectively.

Hospital location was not a significant determinant of outcome ($p > 0.05$) when mortality was used as an end point (Table II and III). Hospital volume as well as individual physician volume showed no statistically significant differences when compared with each other ($p > 0.05$, Tables II and III). A trend toward better outcome was observed in complex CABG procedures when suburban hospitals and physicians were compared with their low-volume urban counterparts; however, no statistical difference was observed ($p < 0.07$, Tables II and III).

DISCUSSION

The development of easily obtainable preoperative criteria for the assessment of operative risk is a desirable goal. Statistical tools for the identification and validation of incremental risk factors are well established.¹³ The data bases employed for such analysis can be divided into three basic categories: patient-related data, such as laboratory and functional data, which are dependent on the patient population; interventional data, such as choice and timing of operation and operative technique, which are dependent on the physician; and postinterventional data, such as outcome, length of hospital stay and treatment-specific data, which are dependent on institutional performance and guidelines.

In cardiac surgery, operative techniques are fairly consistent throughout all institutions.¹⁴ Thus, the patient-re-

lated and institutional-dependent data remain paramount for comparison and analysis of patient outcome in cardiac surgery. The goal of academic institutions is to define the objective patient-related and institutional-dependent factors that affect operative risk. Third party payers and governmental agencies, however, have recently initiated outcome analyses using risk stratification in an attempt to show a better outcome for high-volume centers and physicians with the purpose of maximizing the financial return on their investment.¹⁵⁻¹⁷

It is difficult to compare results between institutions since the differences in preoperative selection and postoperative methods cannot be reliably quantified at present. Criteria developed at one institution may present a distorted view when applied to another institution because of subtle differences in treatment and population. Conclusions based on high- and low-volume classification of hospitals and physicians are misleading when they imply that limiting CABG operations to high-volume centers and physicians improves outcome.

The findings of this geographically localized study, indicate that low-volume centers and physicians can achieve equal survival rates when compared with that of high-volume centers and physicians, regardless of location or complexity of the CABG operation. These findings demonstrate that a lower CABG volume does not translate into higher mortality.

Thus, we conclude the following: Low-volume institutions and physicians can have equal success as compared to high-volume institutions and physicians in terms of mortality rates for CABG operations; preoperative risk

TABLE II. Probability Analysis of Hospital Data

Hospital Volume/Location	CABG Operations*		
	Simple	Complex	Combined
Low volume vs high volume	0.10	0.14	0.43
Suburban vs urban	0.21	0.11	0.43
Low volume suburban vs low volume urban	0.16	0.45	0.27
High volume suburban vs high volume urban	0.55	0.16	0.39
Low volume suburban vs high volume urban	0.35	0.60	0.35
High volume suburban vs low volume urban	0.15	0.06	0.51

* Numbers represent the level of significance calculated using Fisher's exact probability test to calculate p values (significance = $p < 0.05$).

TABLE III. Probability Analysis of Physician Data

Physician Volume/Location	CABG Operations*		
	Simple	Complex	Combined
Low volume vs high volume	0.24	0.55	0.53
Suburban vs urban	0.21	0.11	0.41
Low volume suburban vs low volume urban	0.36	0.07	0.40
Low volume suburban vs high volume urban	0.44	0.19	0.45

* Numbers represent the level of significance calculated using Fisher's exact probability test to calculate p values (significance = $p < 0.05$).

criteria developed in one institution should be applied with caution to nonhomogenous patient populations; mortality may not be the sole predictor of outcome; finally, hospital location does not have an adverse affect on the outcome of coronary artery bypass grafting operations.

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Optimal therapy of cryptococcosis in patients with the acquired immunodeficiency syndrome

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ABSTRACT. Although amphotericin B (AB) is the primary therapeutic agent for cryptococcosis complicating the acquired immunodeficiency syndrome (AIDS), the total dose administered is extremely variable, and the end point of therapy has not been well defined. Since these patients require life-long suppressive therapy following the primary therapy, the definition of treatment "end point" becomes crucial.

To delineate more effective treatment approaches, we reviewed the medical records of 48 patients with cryptococcosis complicating AIDS. Fever (81%) and headache (77%) were the predominant symptoms. A clinical response to AB (defervescence and resolution of symptoms) was noted in 46% of the febrile patients. The cumulative AB dose administered to the time of clinical response was variable (0.1-1.76 g), but was noted early in the majority of the patients (<0.4 g). Repeat fungal cultures from the initial positive site for *Cryptococcus neoformans* (CN), obtained after observation of the clinical response, were negative in 7/7 patients. Nosocomial bacterial infections were quite common and often complicated intravenous AB therapy. Bacteremias were documented in 10/14 febrile episodes occurring during AB

therapy in the 22 patients with an initial clinical response. Bacteremias were identified in 6/21 patients who failed to defervesce with AB therapy. *Staphylococcus aureus* (N = 9) and *Salmonella* species (N = 2) were the most common pathogens causing bacteremia.

An algorithm for the treatment of cryptococcosis complicating AIDS may shorten the duration of primary intravenous AB therapy. This might reduce secondary infectious complications and the costs of hospitalization.

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Amphotericin B(AB), flucytosine, and more recently, fluconazole have produced variable success in the treatment of cryptococcosis complicating the acquired immunodeficiency syndrome (AIDS).¹⁻⁵ Fluconazole appears to be the most attractive azole alternative to AB because of its high level of penetration into cerebrospinal fluid, good absorption after oral dosing, and long half life, allowing for daily administration.⁵ Two recent studies have shown the effectiveness of oral fluconazole in long-term suppressive therapy.^{2,3} However, in one of these studies² primary therapy with fluconazole (without prior AB therapy) was unsuccessful in 2/4 patients. Until the results of ongoing trials are known, AB will continue to be the mainstay of therapy.

Even though it is frequently used, the total dose of AB administered is extremely variable (0.9-5.08 g), and the end point of therapy has not been defined.¹⁻⁴ Kovacs et al¹ could not demonstrate a clear relationship between the total AB dose administered and clinical or microbiologic

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outcome, and thus could make no recommendations concerning the optimal total dosage or duration of therapy. The necessity for prolonged intravenous drug administration in these patients predisposes them to the risk of nosocomial bacteremia. Jacobson et al⁶ noted that AIDS patients are at increased risk of developing *Staphylococcus aureus* bacteremias. In their study, an indwelling intravenous catheter was identified as the risk factor and source for this bacteremia in 16/22 patients. Eight of these 16 patients with staphylococcal bacteremia were receiving intravenous AB. The present study was initiated in an attempt to identify the appropriate duration of primary intravenous AB therapy and the associated complications.

PATIENTS AND METHODS

Forty-eight patients were proven to have cryptococcosis complicating AIDS by positive cultures of *Cryptococcus neoformans* (CN) from one or more sites during an 18-month period (July 1, 1987–December 31, 1988) at two university affiliated municipal hospitals in Brooklyn, NY. Medical records were retrospectively reviewed by one of the authors (VC). Information regarding the following was collected on standard forms: patient's age, sex, risk factors for AIDS, symptoms, signs, routine laboratory data, serum cryptococcal antigen titer results, initial and subsequent isolation sites of CN, cumulative dose of AB required for clinical response (defervescence and resolution of symptoms), results of investigations (specially isolation of other pathogens and repeat cultures of CN) initiated in the event of lack of defervescence or recurrence of fever, and complications attributable to intravenous AB therapy. The diagnosis of AIDS was made according to the criteria of the Centers for Disease Control.⁷ Serum and cerebrospinal fluid (CSF) cryptococcal antigen titers were determined by the latex agglutination test (Metpath Laboratory, Teeterboro, NJ). The study was limited to the events of acute hospitalization.

Fever in patients with cryptococcosis can be due to cryptococcal infection, intravenous AB therapy of cryptococcal infection, or another concomitant infection. Fever associated with intravenous AB therapy is frequent but is not persistent and is temporally related to AB administration. Thus, evaluation of the fever pattern is essential in evaluating clinical response to therapy. Fever pattern was carefully reviewed in all patients. The specific approach for initial diagnosis and for evaluation and management of patients during therapy is delineated in Table I.

TABLE I. Methodologic Approach to Assessment and Management of Patients With Cryptococcal Disease

Step 1. Disseminated cryptococcosis confirmed by	
a.	Culture of <i>Cryptococcus neoformans</i> (CN) from an extra-pulmonary site.
b.	Pulmonary CN isolate plus serum CN antigen titer $\geq 1:8$.
c.	Fluid/tissue considered uninvolved if CN was not identified on microscopic examination and culture was also negative.
Step 2. Delineate indicators of clinical response	
a.	Defervescence (if initially febrile).
b.	Resolution of headache.
c.	Improvement in mental status.
Step 3. Sustained clinical response	
a.	Indicators outlined in 2 a,b,c maintained throughout the course of amphotericin B therapy.
Step 4. Assessment of recrudescence (or new) fever developing during amphotericin B therapy	
a.	Cryptococcal etiology confirmed by positive repeat culture of CN (+/- morphologic demonstration of CN).
b.	Noncryptococcal etiology established by isolation or morphologic demonstration of another pathogen plus response to specific therapy.

Statistical significance of serum cryptococcal antigen titers and India ink positivity of cerebrospinal fluid on survival were calculated by Fisher's exact test. Only a *p* value of less than 0.05 was considered significant.

RESULTS

Retrospective review of the medical records of 48 patients revealed disseminated cryptococcosis complicating AIDS in all 48 patients. Characteristics of these 48 patients are summarized in Table II. The majority of the patients were male intravenous drug abusers. Thirteen patients had another prior or concomitant opportunistic infection. Thirty-nine (81%) of the 48 patients were febrile at presentation, and the temperature was more than 38.3°C in all except three patients. Though headache was the most frequently observed symptom (77%), nuchal rigidity was seen in only 29% of the patients.

The initial positive culture sites for CN prior to the start of therapy are shown in Table III. Cerebrospinal fluid was examined in 46 of 48 patients. CN was isolated from two or more sites in 22 patients, but only from a solitary site in 25 patients (CSF, *n* = 24; blood, *n* = 1). One patient with negative blood cultures refused a lumbar puncture, but CN was isolated from bronchoalveolar lavage. Cryptococcosis was considered to be disseminated in this patient in view of a positive serum cryptococcal antigen determination. Thus, all 48 patients had disseminated disease.

Serum cryptococcal antigen was determined in a total of 28 patients with cryptococcosis prior to the start of therapy. It was positive ($\geq 1:8$) in 25 and negative in 3 patients. Serum cryptococcal antigen titers were more than 1:1,024 in 18 patients, of whom ten died. Antigen titers were negative or less than 1:32 in ten patients, of whom only two died (statistically not significant, Fisher's exact test).

India ink examination was done on CSF in 40 patients, and cryptococci were identified in 33 of them. Twenty-two of these patients died, while all the seven patients with a negative india ink examination survived (*p* = 0.0017, Fisher's exact test).

Clinical Response to therapy. Thirty-nine patients initially were febrile (temperature $>37.8^\circ\text{C}$), while nine were afebrile. Of the 39 febrile patients, 18 had no fever following amphotericin B therapy.

TABLE II. Characteristics of 48 Patients With Cryptococcosis and AIDS

Feature	N (%)
Mean age:	35 years (range 26–54 yr)
Sex:	males
	40 (83)
	females (F)
	8 (17)
AIDS risk:	intravenous drug abuse, F = 6
	38 (79)
	homosexuality
	4 (8)
	heterosexual (born outside USA), F = 1
	3 (6)
Prior/concomitant opportunistic infections:	heterosexual (born in USA), F = 1
	3 (6)
	<i>Pneumocystis carinii</i> pneumonia
	esophageal candidiasis
	3 (6)
	histoplasmosis
	1 (2)
Symptoms and signs:	
Fever:	temperature $> 38.3^\circ\text{C}$
	36 (75)
	temperature 37.8°C but $< 38.3^\circ\text{C}$
	3 (6)
Central nervous system:	headache
	37 (77)
	abnormal behavior/altered consciousness
	12 (25)
	seizures
	5 (10)
	nuchal rigidity
	14 (29)
	focal motor neurologic deficit
	3 (6)
Respiratory:	cough
	13 (27)
	dyspnea
	9 (19)
	chest pain
	5 (10)
Others:	oral thrush
	26 (54)
	diffuse lymphadenopathy
	23 (48)

TABLE III. Initial Culture Sites for *Cryptococcus neoformans*

Sites	Sample Site (N)	Positive N	%
Cerebrospinal fluid	46	45	98
Blood	48	17	35
Sputum	1	1	100
Bronchoalveolar lavage	9	9	100
Pleural fluid	3	3	100
Pleural biopsy	1	1	100
Lymph node	3	1	33
Skin pustule	1	1	100
Two or more sites	48	22	46

The dose of amphotericin B prior to defervescence ranged from 0.10 g to 1.76 g (mean $\pm$ SD = 0.4 ± 0.44 ; median = 0.23). Fourteen patients no longer had fever after receiving less than 0.4 g of AB. Fifteen of these 18 patients were discharged, and three died during therapy. Active cryptococcosis was the cause of death in only one patient. (This patient had received intermittent therapy and, although the total AB administered prior to death was 1.8 g, CSF cultures continued to be positive for CN).

Twenty-one of the 39 febrile patients were not rid of their fever with AB therapy. Fourteen of these 21 patients received less than 0.4 g of AB before death (N = 13) or discharge against medical advice (N = 1), while seven patients completed therapy with more than 0.4 g of AB before death (N = 2) or identification of another infection responsible for the persistent fever (N = 5). Another infection contributed to morbidity or mortality in ten of these 21 patients who failed to defervesce with AB therapy. Bacteremias (*Staphylococcus aureus* = 5, *Klebsiella pneumoniae* = 1, *Streptococcus pneumoniae* = 1, *Clostridium perfringens* = 1) occurred in six patients. *Pneumocystis carinii* pneumonia, *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare*, staphylococcal pneumonia, aspiration pneumonia, and bacterial pericarditis (all one each) accounted for the other coexistent infections in these ten patients. Nine patients were initially afebrile (temperature $<37.8^{\circ}\text{C}$). Five of them died;

Clinical response (CR) to intravenous AB therapy

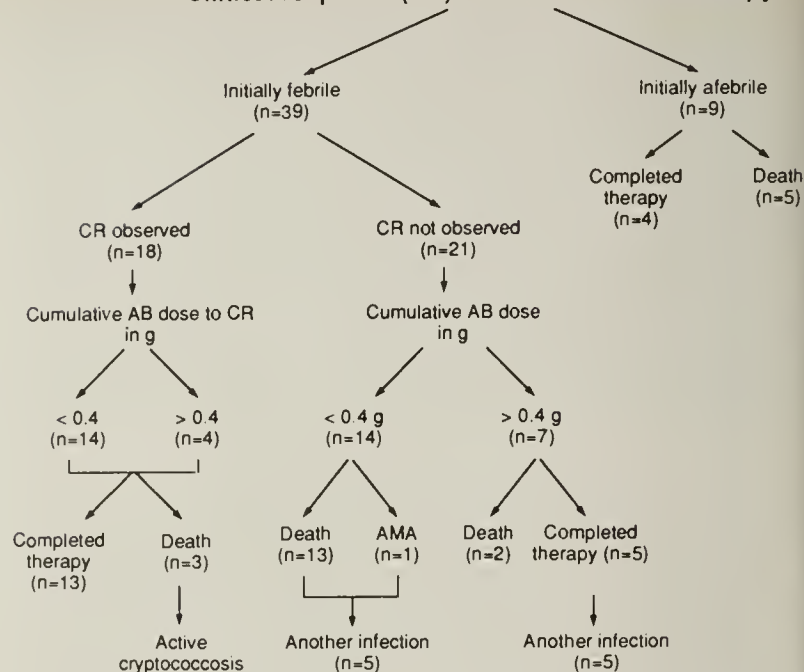


FIGURE 1. Clinical response (CR) to intravenous amphotericin B (AB) therapy.

four completed the therapy and were discharged. Figure 1 summarizes these observations.

We analyzed the cause of elevated temperature ($>38.3^{\circ}\text{C}$ persisting for more than 48 hours) in all patients who had initially defervesced and patients who were initially afebrile. Fourteen febrile episodes in ten such patients were identified. Investigations initiated because of persistent fever revealed a bacterial infection (N = 13) and persistent cryptococcosis (N = 1) as the etiologic basis of the fever. Ten episodes of bacteremia were noted in eight patients. Pathogens causing bacteremias were *Staphylococcus aureus* (N = 4), *Salmonella* (N = 2), *Acinetobacter*, *Streptococcus fecalis*, B

TABLE IV. Results of Reevaluation of Cryptococcal Activity in 12 Patients

Patient	AB DD* in mg	AB Dose at Repeat Culture	Repeat Sampled Sites	Culture Results for CN	Reasons for Repeat Culture	Etiology	AB TD† in mg
1	1,760	2,000	CSF, BAL‡	—	fever	<i>Pneumocystis carinii</i> pneumonia	2,000
2	150	920	CSF	—	fever	arm abscess	1,500
3	250	641	CSF	—	fever	<i>Salmonella</i> sepsis	1,500
4	200	2,000	CSF	—	fever	<i>S aureus</i> sepsis	2,700
5	ND§	1,020	CSF	—	fever	<i>Salmonella</i> sepsis	2,020
		1,620	CSF	—	fever	none identified	
		2,000	BAL	—	fever	<i>Pneumocystis carinii</i> pneumonia	
6	ND	1,300	CSF	—	fever	<i>S aureus</i> sepsis	1,330
7	ND	1,500	CSF	+	fever	cryptococcosis	
		1,650	CSF	+	seizure	cryptococcosis; death	1,800
8	NF	495	CSF	+	fever, seizures	cryptococcosis; death	740
9	100	1,630	CSF	—	EP¶		1,630
10	205	345	CSF	—	EP		630
11	106	1,360	CSF	—	EP		1,601
12	NF	2,070	CSF	—	EP		2,070

* AB DD = amphotericin B dose for defervescence.

† AB TD = amphotericin B total administered dose for primary therapy.

‡ CSF = cerebrospinal fluid; BAL = bronchoalveolar lavage.

§ ND = never defervesced.

|| NF = never febrile.

¶ EP = determine end point of therapy.

hemolytic Streptococci, *Streptococcus pneumoniae* (all one each). In six instances, the source of bacteremia was the intravenous catheter used for AB administration. The non-bacteremic infections were related to the intravenous AB administration site in two febrile episodes (abscess and phlebitis). Persistent cryptococcal infection was identified in one patient by positive CSF cultures for CN. This patient had received AB intermittently, and this perhaps led to ineffective therapy.

There were 12 patients who had a repeat evaluation of the initially positive CN culture site for CN while on AB therapy. Table IV outlines the salient features of these 12 patients. Repeat cultures of CSF for CN were negative in ten patients (cumulative amphotericin B dose of 0.345–2.07 g). Bronchoalveolar lavage cultures obtained during therapy were negative for CN in two patients (cumulative amphotericin B dose of 2.0 g). In two patients, repeat CSF culture was still positive for CN after receiving 0.495 and 1.65 g of amphotericin B. Both patients had received intermittent therapy, and the onset of generalized tonic-clonic seizures had prompted the repeat CSF examination.

DISCUSSION

Cryptococcus neoformans is the most common fungal pathogen causing life threatening infections in AIDS patients.⁴ Therapy in this population includes primary and suppressive phases. Suppressive therapy should be continued for life in this patient population because the relapse rate is high, and survival is reduced without therapy.^{1,8,9} Primary therapy has consisted of daily intravenous AB alone or with oral flucytosine. In patients with AIDS, the addition of flucytosine appears to offer no advantage, yet poses a risk of cytopenia.⁹ Primary therapy with oral fluconazole has been tried recently in four patients with limited success.² Three of these patients had CSF cultures still positive for CN after eight weeks of therapy. Fluconazole has been successful for suppressive therapy,^{2,3} but until the results of trials comparing fluconazole to AB become available, AB will remain the mainstay of primary therapy for cryptococcosis. The optimal total dose of AB and the ideal duration of primary therapy are unknown, though most investigators aim for a 1.0 g minimum total dose.⁴ The end point of primary therapy may vary depending on host response, thus the duration of primary therapy should be determined by objective criteria.

Of the 39 patients reviewed here who were initially febrile, 18 patients (46%) were rid of fever with AB therapy. Defervescence was observed early (cumulative AB < 0.4 g) in the majority (N = 14) of these patients. Clinical response to therapy was not noted in 21 patients (54%), and 13 of them suffered an early death (cumulative AB < 0.4 g). Another infection, which may have contributed to the lack of clinical response, was identified in 10/21 patients (47.6%) who failed to defervesce. Thus, in the majority of patients with cryptococcosis complicating AIDS, an early clinical response should be expected with AB therapy (<0.4 g). Absence of such a response should prompt investigations to identify other infectious causes of the fever and to confirm the adequacy of anticryptococcal therapy by repeat culture of the initially infected site.

Seven of the 18 patients who defervesced with AB therapy had a repeat culture negative for CN from the initial positive site. The total AB dose received between the initial clinical response and "obtaining a negative culture" varied from 0.14 g to 1.8 g. This variability makes it difficult to specify rigidly the best time to obtain the second culture. Eng et al¹⁰ noted that initially infected body fluids

became culture negative in ten patients after only one week of AB therapy. A daily AB dose of 0.7 mg/kg/day will most likely have been attained at the time of clinical response. Seven additional days of intravenous AB (0.7 mg/kg/day) after defervescence adds 0.34 g (for a 70-kg individual) of AB. Reculture of the initial infected site is likely to be negative for CN at that point. Patient 10 (Table IV) received only 0.14 g after clinical response, and yet repeat CSF culture was negative. If the repeat culture one week after clinical response is negative, this may serve as the end point for primary therapy and a starting point for suppressive therapy. A shortened duration of intravenous AB therapy may decrease the "line-associated" bacteremic complications. The effectiveness of such an individualized approach to anticryptococcal therapy must be evaluated prospectively.

Two patients did not defervesce at completion of primary therapy (Table IV; patients 5 and 6); however, therapy was terminated since repeat cultures were negative for CN. Their fevers subsided with treatment of their other specific infections (*Pneumocystis carinii* pneumonia and staphylococcal sepsis). This again emphasizes the presence of other infections as the reason for lack of clinical response when AB therapy has been adequate, as demonstrated by negative CSF cultures. In the two patients in whom CN was repeatedly isolated, both had received intermittent AB therapy. It is possible that intermittent AB therapy may have led to the development of resistant CN.

In this study, 13/14 febrile episodes occurring during AB therapy had a bacterial etiology. *Staphylococcus aur-*

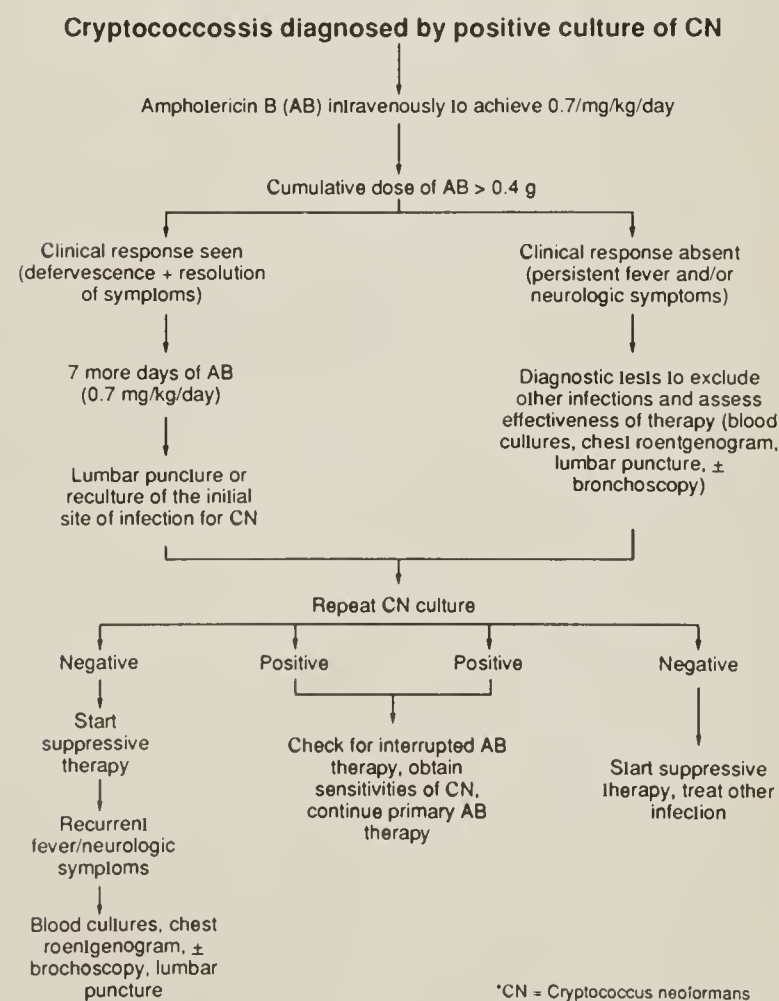


FIGURE 2. Diagnosis of cryptococcosis by positive culture of *Cryptococcus neoformans* (CN).

eus (N = 4) was the most common pathogen to cause bacteremia. Infection was related to the intravenous AB administration site in eight febrile episodes. Bacteremias were also identified in six patients who failed to defervesce with AB therapy. *Staphylococcus aureus* (N = 5) was also the most frequently isolated agent in these patients. A bacterial (N = 18), mycobacterial (N = 1), and/or parasitic (N = 1) infection was present in 19/31 patients who failed to defervesce or had recurrence of fever while being treated with AB for cryptococcosis. Morbidity associated with this high incidence of bacterial infection may be reduced if the primary AB therapy can be effectively shortened.

Our methodologic approach to the evaluation and management of AIDS patients receiving therapy for cryptococcal disease (Table I and Fig 2) permits individualized yet specific planning of treatment and diagnostic interventions without limiting the duration of primary therapy to an arbitrary total AB dose. This permits achievement of goals: shortened duration of primary intravenous AB therapy without loss of effectiveness; reduction in nosocomial bacterial complications; reduced hospitalization; de-

fined end point for primary therapy and starting point for suppressive therapy.

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Mary Edwards Walker, MD: The only woman ever awarded the Congressional Medal of Honor

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Mary Edwards Walker, physician, journalist, lecturer, woman's rights advocate, and native New Yorker was the only woman ever to be awarded the Congressional Medal of Honor for battlefield valor. In addition, Walker was a dress reformer, extremely active in an organized movement to gain acceptance for changes in female modes of dress. Both men and women argued that the restrictive corsets, the hoop skirts, and the weight of the clothing prevalent at the time, were all injurious to women.

On June 10, 1982, in her birthplace of Oswego, NY, the US Postal Service honored her with a commemorative 20-cent stamp featuring her portrait and the wording: Dr Mary Walker, Army Surgeon, Medal of Honor.¹

MEDAL OF HONOR: RECEIVED, RETRACTED, REINSTATED

Presidents Abraham Lincoln and Andrew Johnson were both aware of Dr Walker's services. In fact, President Johnson asked the Secretary of War to look into the merits and legal appropriateness of presenting an award to someone never commissioned by the Army. In his 12 page report to the Secretary, the Judge-Advocate commented:¹

"The case of this lady, when her sacrifices, her fearless energy under circumstances of peril, her endurance of hardship and imprisonment at the hands of the enemy, and especially her active patriotism and eminent loyalty are considered, may well be regarded as an almost isolated one in the history of the rebellion; and to signalize and perpetuate it as such would seem to be desirable."

Acting on that recommendation, President Andrew Johnson pinned the Congressional Medal of Honor for Meritorious Service on the diminutive lady, handing her the following citation from the Executive Office:^{2(p53-54)}

Whereas it appears from official reports that Dr. Mary E. Walker, a graduate of medicine, has rendered valuable service to the Government, and her efforts have been earnest and untiring in a variety of ways, and that she was assigned to duty and served as an assistant surgeon in charge of female prisoners at Louisville, Kentucky, on the recommendation of Major-Generals Sherman and Thomas, and faithfully served as contract surgeon in the service of the United States, and has devoted herself with much patriotic zeal to the sick and wounded soldiers, both in the

field and hospitals, to the detriment of her own health, and has endured hardships as a prisoner of war four months in a southern prison while acting as a contract surgeon; and

Whereas by reason of her not being a commissioned officer in the military service a brevet or honorary rank can not, under existing laws, be conferred upon her; and

Whereas in the opinion of the President an honorable recognition of her services and sufferings should be made:

It is ordered, That a testimonial thereof shall be hereby made and given to the said Dr. Mary E. Walker and that the usual medal of honor for meritorious services be given her.

Given under my hand in the city of Washington, DC this 11th day of November, AD 1865."

Andrew Johnson, President

By the President:

Edward M. Stanton, Secretary of War

However, that was not the last of it. An Act of Congress of April 27, 1916, stipulated that the award should be made for action "involving actual conflict with an enemy, by gallantry or intrepidity, at risk of life, above and beyond the call of duty."¹ Another Act of Congress of June 3, 1916, required the Army and Navy to review the records of all Medal of Honor recipients since the decoration had first been awarded in 1862 to verify that each one's deeds met the newly revised standards. Originally, the only qualification was that persons "shall most distinguish themselves by their gallantry in action, and other soldierlike qualities."¹ A five man board of retired officers reviewed the 2,625 Medal recipients for the Army. Numbered records were used instead of actual names.¹ Based on the new rules, Dr Walker was disqualified along with 910 others. Her considerable efforts to have the board's decision reversed were unsuccessful. Nevertheless, she refused to return the medals; the Army had sent her a new medal with a modified design in 1907. Dr Walker told the Army board that she would continue to wear both medals: "One of them I will wear every day, and the other I will wear on occasions."^{3(p292)} Dr Mary E. Walker was true to her word and wore her Congressional Medal of Honor every day until her death on February 21, 1919.

Even after her death, the battle continued. There was a further review by the Army Board of Correction of Military Records. This Board ruled that had it not been for her sex, Dr Walker would have been commissioned in 1861.¹

"When consideration is given to her total contribution, her acts of distinguished gallantry, self-sacrifice, patrio-

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tism, dedication and unflinching loyalty to her country, despite the apparent discrimination because of her sex, the award of the Medal of Honor appears to have been appropriate, and the Award was in consonance with the criteria established by the Act of April 27, 1916, and in keeping with the highest tradition of military services."

On June 10, 1977, the Secretary of War accepted the recommendation of the Board and signed an order reinstating Dr Walker's Medal of Honor and correcting the official records.

Coincidentally, William F. Cody, (Buffalo Bill) was also stripped of his Medal of Honor at the same time as Dr Walker in 1917. In July 1989, the Army restored the medal awarded to Buffalo Bill in 1872 for his gallantry as a scout during the Indian wars. These were the only two of the 910 persons stripped of their medals in 1917 to regain their awards.⁴

EARLY YEARS

Mary Edwards Walker was born on November 26, 1832 in Oswego, New York to Alvah and Vesta (Whitcomb) Walker. Her parents were newcomers to New York but traced their roots back to early settlers of Massachusetts. Both parents were teachers and operated a farm on Bunker Hill Road outside of the town. Alvah Walker atypically believed that his five daughters should receive an education, as well as his two sons. He often lectured his daughters about their health being impaired by vice-like corsets and tight fitting clothes. In addition, both her parents were abolitionists. Her father was learned in medicine, had medical texts in his house that Walker regularly thumbed through and may have actually been a nonpracticing physician. Walker probably acquired an inclination to study medicine from him. Both of her parents were supportive of her desire to become a physician despite obvious societal disapproval of women entering the profession.^{2(pp9-12)}

Even six years after Walker received her MD, American society still continued to rail against women physicians. In 1859, as a woman graduated from Starling Medical College in Ohio, the Cincinnati *Lancet and Observer* furiously reprehended the awarding of an MD degree to a woman:^{5(p571)}

"Why not grant the degree to sucking babes? There never was a woman fitted to practice medicine, surgery and obstetrics, no matter how long she may have studied. The duties of the physician are contrary and opposed to her moral, intellectual and physical nature."

Continuing and reacting to the fact the eclectic medical schools refused to admit women students:

"Is it then left for a respectable school to so far insult all gentlemen in the profession as to admit to the Temple of Aesculapius those who have no right it?"

As her sisters had before her, Walker attended the Falley Seminary in Fulton, NY. She left the Seminary in 1852 and then taught school at Minetto, NY for about two years while she saved her money and crystallized her plans to become a physician.⁶

MEDICAL THEORIES AND PRACTICES IN THE 1800s

Medical practice during a large part of the 1800s was a hodgepodge of unorthodox theories, irregular healers and

dubious remedies. Physicians often made diagnoses without the benefit of a clinical thermometer, a stethoscope, and without taking the pulse. One treatment mode involved reducing the "convulsive action" via blood-letting and/or the use of calomel for purging.⁷⁻¹⁰

Sylvester Graham and his adherents in the popular health movement advocated a regimen with a no-meat diet, no tea, no coffee, no alcohol, fresh air, exercise, cleanliness, cold bathing, and the avoidance of tightly laced corsets.¹¹

Another treatment modality emerged when Samuel Thomson patented his medical mixtures in 1813 using vegetable drugs in a "botanic system" to cure illnesses. Medical botanists sought to demystify and deprofessionalize orthodox medical practices. This reflected a revolt against the alleged overuse of bleeding, mercury, antimony, harsh purgatives, and salts. Orthodox medical treatment was viewed as a lethal combination of depletion and poisoning: "The seeds of disease and death, are sown in the vitals of society, by the use of poisonous medicines."^{12(p70)}

Augmenting the botanic theories, Drs Alva Curtis and Wooster Beach founded the American Eclectic Medical Association in 1848. In an extensive history of the American Eclectic Practice of Medicine, Wilder⁵ explains the melding of theories into a therapy for the common people.

Earlier, Dr Samuel Hahnemann founded the American Institute of Homeopathy. In Latin, the slogan was "Simile similibus cura, non contrarium" [Like cures its like, and not that which is contrary.]⁵

The allopathic approach to medical care was stressed on May 2, 1848 as the first annual meeting of the American Medical Association convened in Baltimore. Another New Yorker, Nathan Smith Davis III, MD, who practiced in Binghamton, proposed a resolution to establish medical education standards at the 1845 meeting of the New York State Medical Society. He is credited with being the father of the AMA and was AMA President in 1864 and 1865.^{13(p3-16)}

In addition, patients had a choice of hydropathy, mesmerism, phrenology, spiritualism, or vegetarianism.^{14(p3)}

MEDICAL EDUCATION IN THE 1880s

Despite the harsh criticism of Dr Walker's medical education, her training was most likely average for the times. The alleged "medical" criticism to which she was subjected may be attributed to the deep-seated prejudices against female physicians and the Victorian concepts of appropriate behavior for "genteel" women.

An 1867 report of the American Medical Association Committee on Medical Education criticized the state of professional medical instruction:^{15(p363)}

"The curriculum of instruction should be materially, if not completely, reformed. It has undergone no thorough improvement except in a very few of the schools, during the last half century. It is, in fact, essentially the same now as it was at the death of Dr. [Benjamin] Rush in 1813."

A study of medical education before the Civil War found that even the "more firmly established institutions including the University of Pennsylvania School of Medicine, the College of Physicians and Surgeons of Columbia University, University of the City of New York Medical

Department, Jefferson Medical College and Harvard University's Medical Department fell below the peaks of scientific advance."¹⁶(pp416-421)

Charles W. Eliot, President of Harvard University, pointedly described medical education in 1869:¹⁷(p27)

"There were no requirements for admission to our medical schools . . . a young man had nothing to do but register his name and pay a fee . . . The total period of required attendance for the degree of Doctor of Medicine did not exceed, in the best of schools, three winter terms of four months each. The main means of instruction were lectures, surgical exhibitions in large rooms appropriately called theatres, crude dissecting rooms with scanty supervision, and clinical visits in large groups . . ."

Until Eliot arrived, "The Harvard Medical School was a poor thing, unworthy to be associated with Harvard College . . . It was to speak plainly, a money-making institution not much better than a diploma mill."¹⁸(pp87,90) Eliot objected to awarding the MD degree to Harvard students who passed only five of nine ten minute "ridiculously easy" oral examinations. He suggested written examinations to Dr Henry J. Bigelow, Professor of Surgery and the leader of the conservatives at the medical school. Bigelow replied: "The students should not be expected to pass written examinations since half of them could hardly write."¹⁹(pp28,35)

By 1899, there were 156 schools of healing with 24,119 students. Despite the misgivings about medical education, only three states (Alabama, North Carolina, Virginia) required more than a diploma as evidence of competency to obtain a license to practice.¹⁴(p10-11)

WALKER'S MEDICAL EDUCATION

Just after her 21st birthday, in December 1853, Mary Edwards Walker was accepted as a medical student by the Syracuse Medical College, which was not connected with Syracuse University. This school emerged from a consolidation of two earlier eclectic medical colleges in New York. Relevantly, the predecessor Central Medical College (Syracuse, NY) was the first medical school to adopt a definite policy of co-education in October 1849.⁹ In February 1850, Central Medical College graduated the second woman physician in the United States, Dr Lydia Fowler.²⁰

Only six years earlier, in 1847, Elizabeth Blackwell was the first woman accepted to an obscure medical school in Geneva, NY. After 15 months of study, she graduated as a doctor of medicine on January 23, 1849.²¹

When Walker entered medical school, upstate New York was a stronghold of Thomsonian botanic medicine.⁹ Syracuse Medical College opened in 1851 with a tenet that "nothing should be used as a remedy that will injure the human constitution, and that all means used should have a direct tendency to sustain and not depress the vital powers."²² A faculty of nine physicians included the founder of the college, Dr S. H. Potter and Drs Vincent A Baker, William H. Burnham, David Calkins, William Paine, E. H. Stockwell, and A. R. Thomas. In addition, Dr Wooster Beach gave lectures on the theory and practice of medicine and Dr S. O. Gleason on the water-cure.⁵(pp580-584)

A course of instruction consisted of three terms of 13

weeks each. Between terms, students worked (interned) with practicing physicians to gain experience. Walker took a conglomeration of imposing courses in anatomy, surgery, the practice of medicine and medical pathology, obstetrics, diseases of women and children, physiology, materia medica, therapeutics and pharmacy, chemistry and medical jurisprudence. Tuition was \$55 per term plus \$5 for matriculation and \$15 for graduation with about \$1.50 a week for room and board.²(p16.)¹⁷ With an expenditure of about \$253.50 and 18 months of study for her medical education, Walker became Dr Walker in June 1853, the only woman in the graduating class. She joined woman physicians with similar training including Dr Harriet Austin, Dr Ellen Harman, Dr Lydia Hasbrouck, and Dr Lydia Stowbridge.²³ In fact, Dr Walker wrote many articles for *The Sibyl*, a dress reform magazine, edited and published by Dr Lydia Hasbrouck of Middleton, NY.¹⁸

Following her graduation, Walker married her classmate Dr Albert E. Miller on November 16, 1853. Keeping to her beliefs, Walker was married in trousers and dress coat, and the promise to "obey" was omitted from the vows. Dr Miller had already opened an office at 60 Dominick Street in Rome, NY, and Dr Walker joined him supposedly to concentrate her clinical efforts in obstetrics and gynecology.⁶ However, the marriage was short-lived. Walker never gave up her maiden name, saw male patients, and was certainly not subservient. In addition, her husband seemed to have a nonclinical proclivity for women and proved to be unfaithful. Walker ordered him out in 1859 and they never lived together again. In the summer of 1860, Walker moved to Delhi, Ohio, the Reno of the era, for a divorce. However, she did not complete the requirements and her divorce did not take place until 1869.²(p25.)¹⁸

In the Spring of 1862, during a lull in her war-time activities, Dr Walker attended the Hygeio Therapeutic College in New York City. This water-cure medical school was chartered in 1857 by Dr R. T. Trall, ²⁴(pp13-14) a hydropath. By 1861, the school had graduated 200 students, about 50% of whom were women. Mary G. Nichols, also a water-cure zealot, founded an uncharted predecessor healing school, the American Hydropathic Institute in 1851. In her inaugural address Nichols²⁵ spoke about women as physicians: "Women are particularly fitted to practice the art of healing . . . because of the tenderer love, the sublimer devotion, the never to be wearied patience and kindness of women."

Nichols published a book entitled *Experience in Water-Cure*.²⁶ She regularly wrote articles for Dr Trall, editor of the *Water-Cure Journal*, whose masthead slogan was "Wash and Be Healed."²⁷ Water therapy had great appeal for women because practitioners strived to treat feminine ailments naturally.²⁸ To that point, Nichols stated that "Gestation and parturition are as natural functions as those of digestion."²¹(p73)

Although the curriculum could only be considered a refresher or postgraduate training, Dr Walker received another medical diploma on March 31, 1862. Instruction included lectures and a few clinics at Bellevue Hospital. This unconventional medical school did have a woman faculty member; Dr Huldah Page was a professor of

physiology, hygiene, and obstetrics.¹⁷

In a letter to the editor of the *New York Medical Journal* in 1867, Dr Roberts Bartholow²⁹ recalled examining the medical qualifications of Dr Mary Walker during the Civil War. The Medical Director of the Army of the Cumberland had appointed Dr Bartholow to a medical board to recommend a decision as to her employment as a medical officer:

She betrayed such utter ignorance of any subject in the whole range of medical science, that we found it a difficult matter to conduct an examination . . . she had no more medical knowledge than any ordinary housewife . . . She had never been, so far as we could learn, within the walls of a medical college or hospital, for the purpose of obtaining a medical education.“

In his spiteful letter,^{30(p70)} Dr Bartholow concluded that Mary Walker's medical appointment was a cover-up for her true activities as a spy.

Brussel,⁶ a physician reviewing Walker's life in an 1961 article, says “that her medical training was a diplomamill, once-over-lightly affair cannot be doubted.” He also says that “she took time out from her war-time service to garner another *phony M.D. degree* . . .” (emphasis added)

WALKER'S CIVIL WAR MEDICAL SERVICE

Prior to the outbreak of the Civil War, a small ad appeared in the Rome, NY *Sentinel* of March 14, 1860:^{2(p191),17}

FEMALE PHYSICIAN

Dr. Mary Walker has removed to No. 48 Dominick Street opposite the “Arcade,” over Messrs. H. S. & W. O. Shelly's Clothing Store.

The Doctor expresses her gratitude to the Romans for their liberal patronage, and solicits a continuance of the same.

Office hours: 7 to 8 A.M., and 1 to 3 and 6 to 8 P.M.

Referring to the ad, the newspaper added: “Those who prefer the skill of a female physician to that of a male, have now an excellent opportunity to make their choice.”

There was considerable rivalry among physicians for patients and Walker's practice did not flourish. In fact, Walker quickly gave up her meager practice in Rome to go to Washington in the Fall of 1861, right after the first battle of Bull Run. She applied to Surgeon General Clement A. Finley for a commission as a medical officer. Without waiting for the outcome, she volunteered to care for wounded and sick soldiers under Dr J. N. Green at the makeshift Indiana Hospital on the unfinished top floor of the US Patent Office. Although she worked without pay, Walker did wear an officer's blue uniform and acted with the knowledge and consent of the Army.^{17,18} Brussel⁶ characterizes her as “a whirling efficient combination of physician, nurse, orderly, mail clerk, Red Cross worker, and social service investigator.” She also served at the Forest Hall Prison in Georgetown, and in tent hospitals at Warrenton, Fredericksburg, and Chattanooga. Her activities captured the imagination of a *New York Tribune* reporter who wrote a colorful, and most likely exaggerated, description of her war-time service.^{1,2(p39)}

Among the unmarshalled host of camp-followers of the army, not the least noteworthy personage is Miss Mary E.

Walker, or “Dr. Walker” as she is usually styled . . . She can amputate a limb with the skill of an old surgeon, and administer medicine equally as well. Strange to say that, although she has frequently applied for a permanent position in the medical corps, she has never been formally assigned to any particular duty . . . She is at present temporarily attached to the Sanitation Commission, whose headquarters are at the Lacey House opposite Fredericksburg.

We will add that the lady referred to is exceedingly popular among the soldiers in the hospitals, and is undoubtedly doing much good.”

In January 1864, Walker wrote directly to President Lincoln asking to be assigned to the female ward of Douglas Hospital. On January 16, 1864, the President replied: “If they [Medical Department of the Army] are willing for Dr. Mary Walker to have charge of a female ward, if there be one, I also am willing.” However, President Lincoln would not “with strong hand, thrust among them anyone, male or female, against their consent.”^{2(p49)}

Toward the end of January 1864, she was sent to Chattanooga, Tennessee, for assignment to the 52nd Ohio Volunteer Infantry Regiment, replacing its Company Surgeon who had died unexpectedly. Finally, she was commissioned on March 11, 1864, as an Assistant Surgeon at \$80 per month. During that tour of duty, on April 10, 1864, and while she was caring for starving and poverty-stricken people in enemy territory, Walker was captured by confederate soldiers. She was transported to Castle Thunder, a political prison on Cary Street in Richmond, Virginia. She remained there for four months until August 12, 1864 when she was exchanged for a six-foot confederate surgeon from Tennessee.

Following her release from prison, Walker received \$432.36 for about five months of service as a contract surgeon in September 1864; she was in prison for four of the five months. By the 22nd of September, Walker was the medical officer at a Women's Prison Hospital in Louisville, Kentucky. Six months later, on March 22, 1865, she was placed in charge of an orphan asylum in Clarksville, Tennessee, and was also responsible for refugee families in the area. Later, Walker was transferred to Washington and her contract was terminated on June 15, 1865. Due to a war-time eye injury attributed to partial muscular atrophy while imprisoned, she was awarded a disability pension of \$8.50 per month starting June 13, 1865. Her injury was painful, did not respond to treatment, and resulted in her wearing glasses. After considerable agitation over the years, that pension was raised to \$20 per month in 1899.

LECTURER, LOBBYIST, AUTHOR, AND PHYSICIAN

After the Civil War, Walker's medical practice took second place to her other activities. She was usually in her Washington medical office on L Street NW near the corner of Tenth³¹ from September to June and in Oswego from July to September.

In 1866, Walker sailed to Great Britain with Dr Susanah Way Dodds of St. Louis as an invited delegate to the annual meeting of the Society for the Promotion of Social Science. While in the audience at the October meeting, Walker was invited to address the meeting and spoke on prevention of infanticide, against capital punishment,

dress reform and equal rights for women. She also visited a number of hospitals and facilities. James Edmunds, the President and principal promoter of a female medical society, arranged for Walker's appearances hoping to facilitate the acceptance of women in medicine.

At precisely eight o'clock on November 20, 1866, Walker gave her first lecture at St James' Hall in London. Her subject was "The Experiences of a Female Physician in College, in Private Practice, and in the Federal Army."^{2(p65)} British newspapers were quite complimentary about the lecture. They denounced the hecklers in the gallery: "a mob of unruly boys, alleged, we hope falsely, to be medical student (who were) noisy and vulgar (and) even indecent (but she) cowed the gallery-full of stupid gentlemen."^{2(p68),32} Melampus³³ called the behavior "cowardly ruffianism" and the hecklers "drunken costermongers." In concluding, Melampus said about women, "Let them study medicine if they desire it." Glowing newspaper reviews led to an additional 30 lecture invitations¹⁸ including a 10 city Scottish tour arranged by Monson Kyle.^{2(p72)}

However, American medical journals reprinted the less favorable comments of their English counterparts. Under "Varia" the *New York Medical Journal*³² culled comments from the British professional press citing a particularly picturesque example: "The *Medical Press & Circular*, with a bitterness and intensity of satire surpassed only by its coarseness, styles her the American Medical Non-

descript, and suggests as an attractive subject for her public entertainments, 'Why Not? or, Clitoridectomy and its Uses.'"

After the strenuous lecture circuit, Walker was off to Paris in June 1867 for a visit to the Exposition, sightseeing, and a few hospital visits. Back to London in July, she spoke before the Female Medical Society and the London Dialectical Society before returning to the United States.

Beginning in early 1868, Walker took to the American lecture circuit. She continued to speak about her war experiences and medical activities. Interspersed with her lectures, she fought for dress reform, equal rights for women, and a host of other liberal causes. She gave her impressions of European woman's suffrage to an audience at the Universal Franchise Association in Washington in May 1868. After an introduction by suffragette Belva Lockwood, she lectured on "Pure Love and Sacred Marriage" at Washington's Union League Hall in June 1869. As a member of the Central Women's Suffrage Bureau in Washington, she helped to solicit funds to endow a chair in medicine at Howard University to be filled by a woman professor. In April 1871, Walker and other suffragists attempted to register to vote but were turned away by the election board. Active in New York State politics, she declared herself a candidate for the U.S. Senate in 1881. Her qualifications included a "brain not numbed by drugs, liquor or tobacco."^{2(p106)}

By 1877, Walker switched to wearing male attire including striped trousers, a stiff-bosomed white shirt, frock coat, and high silk hat.¹⁸ However, she did retain her womanly curly hair. In fact, Walker was arrested a dozen or more times, for "masquerading in men's clothes." Even New York City's Police Commissioner, Thomas C. Acton, apologized for such an arrest on Canal Street in mid-June 1866.^{2(pp56-59),31,34}

Between her lecturing and lobbying, Walker wrote two books. In 1871, the autobiographical *Hit* was published with a dedication to: "My Parents, and also to the Practical Dress Reformers . . . and also to My Professional Sisters [Physicians] . . . and lastly to that Great Sisterhood which embraces women with their thousand unwritten trials and sorrows that God has not given to men the power to comprehend . . ." That 180 page book included chapters on love and marriage, dress reform, tobacco, temperance, women's franchise, divorce, labor and religion. Medically, Dr Walker stated that tobacco ruined the digestive system and poisoned every tissue in the body resulting in paralysis and insanity. "The greatest sorrows that women suffer today are those physical, moral and mental ones, that are caused by their unhygienic manner of dressing!"^{35(p66)} She also advocated that a married man be called "Misterer" in as a woman is called "Mrs."^{3(p294),35(p30)}

Seven years later, Walker published *Unmasked or the Science of Immorality*³⁶ covering sex and ethics for men. This amazingly frank book for 1878 ventured into topics suitable for today's tabloids: how men learned about sex, hermaphrodites, male morning sickness, kissing spreads disease, hymens as proof of virginity, seminal discharges and depravity, barrenness and sexual excesses, and social disease. Walker also classified men into six types ranging from the man who respected his wife as he would his honored mother to the man who was constantly on the prowl for victims to satiate his sexual drives.^{2(p88),17}



FIGURE 1. Dr Mary E. Walker in late 1865 wearing a "bloomer" outfit, her Congressional Medal of Honor, and her Extra Assistant Surgeon pin at her neck. (Collection of the National Archives, Library of Congress)



FIGURE 2. Dr Mary E. Walker in full male attire in 1908 with the redesigned Medal of Honor on her frock coat and a rose in her vest. (Courtesy of Charles M. Synder)

Experiencing financial problems and after considerable politicking, Walker was appointed a clerk in the mailroom of the Pensions Office of the Department of the Interior in April 1882. Her work was routine and she reported that she was "sought to give prescriptions and loan small sums of money, and do little offices of kindness that I invariably repsonded to."^{2(p115)} Her supervisor, D. L. Gitt, complained of Walker's excessive absences; she missed 112 days in one year. Her complaints included her eyes, her chest, her right arm and finally the left arm. Gitt labeled her as "violent, high tempered and abusive . . . aggressive and insolent."^{2(p116)} In June 1883, Walker returned to Oswego and shortly thereafter received a discharge notice from Secretary of the Interior H. M. Teller. Outraged, she fought her firing through five months of appeals all

the way up to President Chester Arthur. However, her discharge was upheld and that ended her government service.

Desperate for money, she had only \$8.50 per month from her disability pension, Walker took to the lecture circuit again in 1887. A professional agency, Kohn and Middletown, booked her into dime museums at a fee of \$150 per week.^{17,31} A March 25, 1893 *Toledo Blade* article noted Dr Mary Walker's act on the stage built for freaks: "Other features in the Curio Hall included: Captain Sydney Hinmann, captain of the life-saving crew at Coney Island, with his complete life-saving outfit; Professor Stendell with his experiments in electricity; the Mexican feather workers; and Stephen Stephens and his London Punch and Judy show."³⁷

Using picturesque language and an energetic delivery, Walker spoke on the science of dress, woman's franchise, labor unrest, the evils of tobacco, human electricity, and the curiosities of the brain. At New York's Vine Street Dime Museum, she averred that the constant swaying of crinoline spread over hoopskirts on the hips of women caused nervous afflictions. In 1897, she addressed about 2,000 people attending the first Congress of Mothers; later to become the National Congress of Parents and Teachers.³⁸ Although speaking engagements were infrequent in 1912, Walker even added a lecture on "A Safe and Sane Fourth of July" to protest the deaths and injuries from fireworks.^{2(p145)}

During the 1880s and 1890s, Walker spent less time in Washington, but Oswego did not really become her home until the turn of the century.

Even though Dr Mary E. Walker was out of touch with medicine, she still spoke her mind on professional topics. In 1910, she denigrated the "humbug" theory that germs caused tuberculosis: "No microbes or germs can live in the live tissues of the lungs. They are not the cause of tubercules, but the result of worn-out tissue. Tubercules are formed by smoke, and tobacco smoke is worse than any other kind because the cinders are more poisonous, containing nicotine."^{2(p145)}

In the *Oswego Palladium* of May 9, 1910, Dr Walker revealed how to prevent heart failure caused by overwork, mental strain, or spasmodic coughing. Her remedy: When unusual palpitations occur, place the left hand just below the heart with the fingers pointing to the center of the chest. Place the right hand over the left with the fingers touching the left wrist. Apply pressure until the heart beats normally again.^{2(p145)}

Walker opposed compulsory vaccination for smallpox. In 1911, she testified in Albany before the Health Committee of the New York Senate and Assembly. She contended that the claims for prevention of the disease were grossly exaggerated and that vaccinations were being done for the fees involved. Walker advised onions as a deterrent and supported the proposed McManus-Boylan bill allowing unvaccinated children to attend school when their parents conscientiously opposed vaccination.^{2(p144)}

In October 1913, the annual meeting of the New York State Historical Association met in Oswego. Congressman Luther Mott introduced the 81-year-old Walker to one of the speakers, Assistant Secretary of the Navy Franklin Delano Roosevelt (FDR). Walker spoke to FDR

about her misgivings about the other Roosevelt, but assured FDR that he appeared to be a different kind of person.^{2(p147)}

As late as 1916, Dr Walker expressed her views on infantile paralysis in the *Knickerbocker Press*. Denying that poliomyelitis was contagious, she condemned quarantine and attributed causation in children to their consuming more milk than adults and their inability to shed the poison of tobacco.⁶

As the U.S. entered World War I, Walker fired off a telegram to Germany's Kaiser Wilhelm offering the use of her Bunker Hill farm as the site for a peace conference. Her cablegram was reprinted in full in the *Oswego Palladium* of April 11, 1917. There appears to have been no reply to the offer.^{2(p148)}

Shortly after sending the cable to the Kaiser, Walker fell while climbing the Capitol steps in Washington. She never completely recovered from this severe injury and died about two years later on February 21, 1919 in Oswego at age 86.^{39,40,41}

In Brussel's⁶ 1961 article, "Pants, Politics, Postage, and Physic" he noted that Mary Walker "simply failed each time she attempted her hand at medicine." His professional psychohistorical analysis follows: "Psychiatrically, a review of Mary Walker's history clearly indicates a well-established diagnosis of paranoia, representing a compromise with reality unwelcomingly thrust upon a militant and determined ego that revolted against its sex, rebelling—not in a mere turn to homosexuality—but in an open, and as complete as possible, switch to the opposite sex. At best, Mary Walker was a poorly adjusted and chronically unhappy wretch of a woman." However, that psychiatric analysis did not deter the U.S. Postal Service and others from still honoring Dr Mary Edwards Walker. Shortly after her death, the *Literary Digest* declared that "her eccentric dress drew attention from her real achievements."³⁴ That article quotes the *New York Sun* deploring the fact that "the trousers, frock coat,

starched shirt and collar, and high silk hat, in which she chose to attire her little body, effectively overshadow the work she did."

A number of sources credit Dr Walker with originating the postal card return receipt for registered letters, with improving third class mailing procedures, with advocating the use of the sender's return address to prevent mail from going astray, and with inventing the inside neckband on men's shirts to protect the skin from being rubbed by the collar-button.^{3(p296),6,31,34,42(p352),43(p99)}

These other claims may or may not be true. However, there is no doubt whatsoever about one claim to fame. Dr Mary Edwards Walker was the only woman ever to be awarded the Congressional Medal of Honor.

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FIGURE 3. First day issue, June 10, 1982, of commemorative Dr Mary E. Walker stamp on a postcard. (From the collection of the Oswego County Historical Society)

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Dendritic Cavortings

I think about the golden thought, the soaring dream, the fantasy, the inner sight of beauty,
and see in my imagination sparks and turbulences, breezes and touchings that work
their magic and their messages through spidery dendrite arms and long axonic reachings,
synaptic contacts, chemic and electric, cell-to-cell, that excite or soothe, modulate, negate.

I sense the complex neurologic matrix of the human mind, the spangled creative firmament
of tellers of tales, composers of poetry and song, wielders of brush and paint, shapers of stone,
and the inspired glows that light their skies as lightning does a darkened earth.

If this be true of artistry, what of philosophers and those of more scientific bent?

Less like lightning their neurologic paths, more like streams of brilliant light that course
through fiberoptic threads to bend and turn toward reasoned goals and ends and precepts.

Yet, neither are but sensors of the inner goings on that wake their passions or their thoughts;

the dendrite flash and spark must take at last rousing axon paths that move hand, voice, pen, or brush

to productive ends, and beyond, to receptive hearts and minds that open to the magic of their works.

ALFRED P. INGEGNO, MD

Artificial neural networks: One step too far?

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Understanding the function of the brain is a challenge that is attracting a growing number of scientists from various disciplines. We do not yet understand how the nervous system enables us to see and hear and most importantly learn skills, remember events, plan actions, and make choices. The principal goal of computational neuroscience is to explain how electrical and chemical signals are used in the brain to represent and process information.¹ Artificial neural networks (ANN) try to simulate and to fabricate networks and devices in the spirit of neurobiology, and to solve useful computational problems of the kind that biology does effortlessly. Acknowledging the potential of a computer system that can possibly demonstrate cognitive function is a sobering thought.

Artificial intelligence (AI) covers the entire range of simulated cognitive functions. Our example, the ANN, is a fundamental element of this AI field, and as such it resides in a very early conceptual/development phase. It forms parallels with, and mimics the essence of, human biological computational processes. An interesting thought is, "Will such rudimentary systems evolve in the future into sophisticated bio-like computers possessing more of an understanding of their own wide-reaching impact than we as human developers can possibly imagine?"

The observations and recording of nerve response is not new. Since Galvani and the frog leg experiments of late 18th century, we have been aware of communication between nerves. By the end of the 19th century, Caton and others had demonstrated the significance of the electroencephalogram (EEG) in animals and later visual evoked potential (VEP). Auditory localization was mapped by Larionor. Finally, Hans Berger first reported in publications between 1929 and 1938 that humans had electrical activity in their brains and were therefore similar to other vertebrates.²

Present day computer technology allows the clinician ready access to brain waves (EEG), VEPs, brainstem auditory evoked potentials, and somatosensory evoked potentials. These procedures along with electromyography are good examples of biological neural responses to external stimuli. Accordingly, one can see an ample body of

clinical data and the basis for serious consideration of simulated neurological processes.

Although computing has advanced to solve a wide range of scientific problems providing speed, accuracy, and convenience, the computer in many instances is still unable to solve recognition- and identification-type problems, which in a biological system model appear to be the simplest of tasks.³ Furthermore, the ability to adapt rapidly and learn on the run continues to be beyond all conventional computer systems. These types of problems, such as the development of advanced robotics and controls and AI require an almost cognitive-like capability for the machine.

Recent developments in ANNs have stirred interest in a new and potentially useful approach for solving such problems. Approaches such as those developed by Hopfield et al,^{4,5} have shown that with an array of highly interconnected feedback amplifiers (each amplifier simulating a neuron) it is possible to mimic rudimentary parts of the biological system.

Although there are a number of other architectures employing various means for interfacing with the ANN, (eg, electrical, optical, electro-optical⁶), for our purposes we present a brief description of an ANN with an electrical interface similar to Hopfield et al's. Initially, a set of input signals (dendrites) are applied to the network producing analog-level transitions, which are coupled (synapse) into and between other amplifiers resulting in a dynamically changing set of voltage levels. These levels eventually settle into quasi-stable states, either fully turned on or fully turned off, much as a biological neuron transits from full firing rate to being turned off by synaptic coupling. For the ANN, these states are unique to the given input data set and can be viewed as representing a learning set for that particular input signal ensemble. For a new input signal, the ANN is again started and run, generating a new learning set and so on.

As one might expect, to take on even modest problems, the ANN will require large numbers of discrete electrical inputs, one or more for each amplifier, and a corresponding number of coupling functions. These required connection densities will pose a challenge for present and future technologists.

In such ANN ensembles, variable feedback and synapse-like interconnections provide a self-learning set of in-

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structions, as for example, those derived from a two-dimensional image. These functions are similar to a biological neural network in that all the neurons receive stimulus directly through synaptic couplings, producing potentiality and inhibitory functions at the output of the neural network.

As in most neural networks, the forms and/or coding of the input and output data will in general differ. From the earlier discussions, we said that a two-dimensional image might constitute the input data, and the states of the neuron amplifiers would then represent the corresponding output data or how the neurons responded to the image. The input data "code" in this application is generated by prior data and to that extent is arbitrary. The output data "code" is determined by the feedback network, which is established by the input-controlled couplings, to produce measurable and useful discriminants for different two-dimensional images. Each of these outputs (0 or 1), with regard to position or level in the array, are equal contributors to the outcome of the ANN. Therefore, each output level and position is of equal weight, so that the loss of one output will have only a small effect on the outcome of the process. This is compared to a binary coded word of a digital computer where the loss of one, large bit, such as the "most significant bit," would have a drastic effect on the outcome. These equally weighted terms constitute the learning set of the ANN and are stored in the memory.

Such chaotic decision paths would never be found in a "respectable digital computer." For the respectable computer, even for the little \$1.98 specials, there are set paths and logic sequences, which are invariant and which serve to provide us with the high degree of accuracy and speed we all have come to expect for the solution of narrowly defined problems. It is this very ordered process, conceived by von Neumann et al, that imposes limits on speed of computation vis-a-vis versatility and that is now viewed as a constraint called the von Neumann block. The ANN, on the other hand, appears slower than the digital computer, but it is not constrained by one set of operating rules and has the capacity for rearranging its internal instructions (as does its biologic cousin) on the basis of the stimulus to which it is to respond in a cognitive-like fashion.

Lest one think of ANN only as another type of computer, one should consider its application to medical research. It is interesting to note that the ANN can be afflicted by "neurologic-like disorders." Failures in the couplings (open and short circuits) of amplifiers could exhibit effects similar to those seen in demyelinating disorders. The

effects induced by substances might also be studied. For example, the neuron amplifier in some circuit configurations can "lock up" and produce what in effect appears as an endless loop, analogous to the sustained neuron firing that occurs when certain drugs are administered. Additionally, ANN simulations might be useful in understanding complex, multivariable processes, such as feeding behavior and appetite control. In a process such as this, where multiple individual components have been isolated and studied (eg, brain neurotransmitters, gastrointestinal signals, liver metabolic influences, adipose tissue correlates, external stimuli), ANNs could be used to simulate the extensive integration of these multiple mechanisms, enabling us finally to understand feeding behavior. Simulations by ANNs such as these might aid in future neurological research, allowing insights to the biologic processes that would be otherwise unattainable.

We believe it is timely for the health care community to be aware of these rapidly developing systems. Specifically, it is time that more collaboration among scientists and physicians occur in the overall development of AI systems, as for example presented by ANN.

It is conceivable that, in the way that genetic research is monitored today, in the future AI systems restraints might be imposed on independent research of these new pathways. It is too early to show concern about what the ethicists may find in this future setting, but it is not too early to explore with interest and awe the prospects of such devices in mankind's development. The digital computer will continue to expand its role for general purpose computation and even in the architecture of the AI system. However, for that class of problems requiring cognitive judgment, the ANN in its various forms is likely to go where wise men may not dare to tread!

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Contrasting attitudes in the evolution of surgery for treating ulcerative colitis and Crohn's disease

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With recent progress in the field of immunology, the role of allergy in gastrointestinal diseases has become a topic of increasing importance. This aspect of ulcerative colitis was first appreciated in 1745 when Prince Charles Edward, the Pretender to the British throne, (known as "Bonnie Prince Charlie" to his Scottish Jacobite brethren) developed severe gastrointestinal bleeding ("a bloody flux") associated with ulcerating skin lesions suggestive of pyoderma gangrenosum. Sir Gordon-Gordon Taylor¹ recorded the original description, and John Goligher et al² believed this to be the first recorded case of ulcerative colitis cured by exclusion of milk products from the diet.

Ulcerative colitis and Crohn's Disease represent the two major forms of inflammatory bowel disease seen in the United States, the United Kingdom, Northern Europe, and Scandinavia. Ulcerative colitis is a mucosal disease limited to the large bowel, which may be cured by complete excision of the colorectum. Crohn's disease, a panenteric transmural inflammatory process, may recur at almost any site in the gastrointestinal tract following resection of overtly diseased bowel. This paper examines the sequence of events that led to surgical procedures for treating these complex diseases.

EVOLUTION OF SURGERY FOR ULCERATIVE COLITIS

Surgery for ulcerative colitis has developed over the past century from simple inguinal colostomy and appendicostomy, through ileostomy, to total proctocolectomy today. Although ulcerative colitis was first described as a mucosal ulcerating disease by Wilks and Moxon in 1875,³ it was not until 1893 that a surgical solution to the problem, inguinal colostomy, was attempted by Mayo Robson.⁴ In 1895, Keetley,⁵ in London suggested exteriorization and intubation of the appendix, and in 1902 Weir,⁶ at the Roosevelt Hospital in New York, first performed the operation of appendicostomy. This simple operation required prolapse of the appendix through a small muscle-splitting incision with amputation of the stump within one week. Irrigation of the colon with a sodium bicarbonate solution through a small cecal catheter, with passage of fluid through the colon and out of a large rectal tube, was then carried out.

Although this technique was believed to be successful in some cases, a more effective method, ileostomy diversion

of the fecal stream, was suggested by Allison.⁷ Ileostomy with total diversion of the fecal stream was first carried out by John Brown⁸ in St Louis in 1913; he reported ten cases. Although he closed the distal end of the ileum, irrigation of the distal bowel via a cecostomy with proximal diverting ileostomy became the procedure of choice. Initially, it was believed that the "temporary" ileostomy could be reversed by restoration of intestinal continuity, but it soon became apparent that reactivation of disease could occur, often quite rapidly, requiring reoperation. It also became evident that leaving the colon excluded from the fecal stream was not a satisfactory long-term solution to the problem of active ulcerative colitis. Although the severe symptoms were relieved, continued activity in the colon led to passage of bloody mucus, sometimes with crampy abdominal pains, and even hematochezia. Furthermore, the extra-intestinal manifestations often persisted, and most serious of all, malignant transformation occurred in the excluded colon or rectum. The next logical step was colectomy. Colon resection evolved from a four-stage procedure of sequential ileostomy, right colectomy, left colectomy, and abdominoperineal resection of the rectum (each resection with distal mucous fistula), to a two-stage procedure of subtotal colectomy with ileostomy and mucous fistula.

The early permanent ileostomies were associated with a myriad of complications, and long-term successful outcome was rare. Warren and McKittrick⁹ found "ileostomy dysfunction" in two thirds of patients, usually due to stenosis of the prolapsed serosa-lined terminal portion of ileum. Brooke,¹⁰ in 1952, suggested that eversion of the distal ileum would avoid these problems. This, together with better appliances, resulted in a remarkable improvement in the quality of life for people with ileostomies.

Finally, total proctocolectomy and permanent end "Brooke"¹⁰ or "Turnbull"¹¹ ileostomy became the procedure of choice for relatively healthy patients over the next few decades in most major institutions. Subtotal colectomy and ileostomy continued to be common procedures in severely debilitated patients with anemia and hypoproteinemia associated with major weight loss, as well as in patients with toxic megacolon, severe colitis, or perforating colitis.

Massive hemorrhage, treated in earlier years by total colectomy to remove all bleeding areas, is now treated selectively. Subtotal colectomy is the preferred method of treatment. If the massive hemorrhage originates in the

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rectum, proctocolectomy is mandatory. Every attempt should be made to preserve the rectal segment where possible, so that recently developed reconstructive procedures may be carried out electively at a later time.

The recent two decades have seen the advent of several new techniques to avoid the social disability of a permanent ileostomy, which requires continuous fluid output via an external appliance. The first was an attempt to create a "continent ileostomy," with construction of an intra-abdominal reservoir, reported in 1969 by Nils Kock.^{12[sm]} This reservoir, when successful, would increase in capacity within months, and remain continent as long as the nipple valve did not prolapse. Regular intubation of the nipple valve is required at least three to four times daily for life. However, numerous problems such as prolapse of the nipple valve and fistula complicate this procedure.

Attempts to maintain or reconstruct intestinal continuity obviating the need for either an external appliance or a tube were approached in two ways. Aylett¹³ popularized the "ileorectal anastomosis." This gave satisfactory results in many patients, but the risks of reactivation of rectal disease and of cancer in the long term in the remaining rectal segment persisted. The second, intellectually more satisfying solution was suggested by Sir Alan Parks¹⁴ at St Marks Hospital in London. He carried out total removal of the mucosal disease by proctocolectomy with "coring out" or "stripping" of the distal rectal mucosa and ileoanal pull-through and anastomosis. The latter procedure was first practiced by Ravitch¹⁵ in 1948, with a low ileoanal anastomosis, but was abandoned soon thereafter because of anal incontinence associated with severe perianal excoriation. Similar procedures with coloanal pull-through, with or without formal anastomosis, were carried out by Maunsell-Weir, Black, Bacon, and Turnbull between 1892 and 1952, mainly for distal rectal cancer.¹⁶

Parks et al¹⁴ added a triplicated distal ileal pouch from the distal 60 cm of small bowel, with a long outflow tract which he sutured to the anal mucosa, creating an ileoanal anastomosis. Half of his early patients required intubation of the pouch. This problem was solved for most patients by shortening the outflow tract to 3–4 cm, decreasing the length of rectal mucosa stripped to approximately the same length, and decreasing the size of the pouch from three 15-cm loops to three 10-cm loops. Alternative pouches are the J pouch suggested by Utsunomiya¹⁷ of Japan and now practiced in most major centers in this country; and the W pouch, a 4-loop pouch, described by Nicholls.¹⁸ This technique of constructing of a pelvic ileal reservoir to replace the rectum results in considerable diarrhea and morbidity during early learning, but is becoming the preferred treatment for ulcerative colitis patients who are not debilitated or too old. Recent excellent results by experienced surgeons suggest that this will become the procedure of choice for ulcerative colitis following total proctocolectomy. At present I prefer the J pouch, with the use of the cavitron to strip the rectal mucosa, as described by Heimann et al.¹⁹

EVOLUTION OF SURGERY FOR CROHN'S DISEASE

Following resection of the terminal ileum in 14 patients, as described in the classic paper by Crohn, Ginzburg, and Oppenheimer in 1932,²⁰ physicians at the Mount Sinai

hospital and several groups in Sweden suggested progressively more radical surgery in the hope that this would result in a "cure." Excision of two feet of small bowel on either side of the diseased segment was recommended by Colp and Dreiling,²¹ in 1952. Swedish surgeons suggested that "radical" resection of an additional 10–35 cm would result in a lower postoperative recurrence rate,^{22,23} but this was found to be fallacious. In the "bypass procedure," a new concept developed at the Mount Sinai Hospital, an ileotransverse colostomy "in-continuity" was created. Subsequently, transection of the ileum proximal to the disease, known as "exclusion," was carried out. Garlock²⁴ believed that this would give lower recurrence rates but this too was found to be erroneous.²⁵ In addition, the bypassed segment produced complications; recurrent abscess, perforation, and cancer in the excluded loop.²⁶ Today, bypass is used only for the critically ill patient in whom resection is considered to be hazardous. These bypassed segments should be removed as early as possible. Many surgeons do not use the bypass procedure at all, and will use a defunctioning ileostomy if resection is not possible.

The subsequent history of resectional surgery for obstructing disease has been characterized by removal of progressively smaller segments of bowel, decreasing from 60 cm²¹ to 10 cm,^{22,23,27} and ultimately to limited resection today—2-cm margins of normal bowel on either side of the diseased bowel. The logical outcome of removing less and less normal bowel, both proximal and distal to the area of disease was suggested by Lee²⁸ and subsequently by Alexander-Williams.²⁹ Could the diseased bowel be left in situ, and strictured areas of bowel opened up by some form of enteroplasty? This has been successful in well over 200 patients in England^{30,31} and America,³² in whom various forms of "strictureplasty," usually similar to the Heineke-Miculicz pyloroplasty, have been constructed. Some surgeons have utilized a Finney-type procedure,³¹ but it is doubtful that preserving a long segment of diseased bowel and forming a large dilated saccular aneurysmal pouch will prove to be judicious.

There is a definite, albeit limited, place for strictureplasty in Crohn's disease with stricture. Strictureplasty should be reserved for three clinical situations: patients with multiple short strictures; patients with fewer strictures in an extremely short bowel; and patients with numerous widely separated strictured areas throughout the jejunum and ileum. Contraindications are strictures associated with solitary and multiple fistulae, long solitary strictures, multiple strictures in close proximity within a single segment of bowel, disease located centrally in the jejunoileum if the proximal and distal small bowel are completely normal, and the presence of carcinoma. The long-term reoperation rates and cancer rates are not known. Nevertheless, in my experience with over 85 strictureplasties in 19 patients, there is low morbidity and high success rate with no early postoperative perforations or fistulae (rates of ~4%–5% have been reported). Subsequent surgery was required in three patients: one patient had 29 strictures and required surgery for a new stricture proximal to an enteroanastomosis; one for local abscess formation; and one for a perforated duodenal ulcer.

Resection of diseased bowel is the key to management

of the perforating forms of Crohn's disease.^{25,33} Abscesses should be drained, followed by definitive resection.³⁴⁻³⁶ Fistulae generally require local resection of the diseased segment following medical therapy of variable duration.^{37,38} Free perforation requires immediate laparotomy, resection, and diversion.^{39,40}

CONCLUSIONS

Many years ago, surgery for inflammatory bowel disease was approached with fear and trepidation, as the diseases were poorly understood. Surgical procedures were slowly introduced into the therapy for ulcerative colitis and Crohn's disease. Initially the morbidity and mortality was high, usually due to toxic megacolon, perforation, and massive hemorrhage in ulcerative colitis, and perforation and abscess in Crohn's disease.

The limited surgery of ulcerative colitis of a century ago gradually evolved to the radical approach used today, with the ultimate goal being a cure. Mortality and morbidity have lessened remarkably over the past century with earlier surgery, better medical therapy, and improved anesthesia and surgical technique. The unhealed perineal wound, postoperative sepsis, and impotence are rarely seen today in major institutions that treat patients with this disease on a routine basis. Finally, the reconstructive phase, with pelvic pouch and ileoanal pull-through, has created a new set of surgical problems, and a new list of postoperative complications that are now being overcome. These procedures are fortunately associated with low mortality because of improved surgical and anesthetic technique. Nevertheless, despite these tremendous advances in patient care for inflammatory bowel disease, death may still occur. In ulcerative colitis, fulminating colitis, toxic megacolon, massive hemorrhage, free perforation, and cancer still result in significant mortality when surgical intervention is delayed. Similarly, in Crohn's disease, intra-abdominal and retroperitoneal abscess, perforation, and cancer may be lethal. In these circumstances, surveillance and early surgical intervention is mandatory and will reduce mortality.

The pathophysiology of Crohn's disease, both panenteric and segmental, differs from that of ulcerative colitis, a continuous disease limited to the colon. Because of high postoperative recurrence rates in Crohn's disease, and the possibility of cure in ulcerative colitis, surgery has evolved in opposite ways in these two diseases: from limited to radical surgery in ulcerative colitis (with reconstruction), and from radical to minimal surgery in Crohn's disease.

In the near future, there will be advances in the technical aspects of the surgery of ulcerative colitis, especially in those of pouch construction. The ability to lengthen the mesentery of the small bowel so that anastomosis at the anus can be carried out without tension remains to be perfected. Major steps have been taken over the past ten years in this regard. Reconstruction in the obese patient, and in the patient with a short mesentery remains a challenge. A small bowel autograft using an isolated segment with revascularization at a lower level may be possible in the future.

In Crohn's disease, extensive jejunoileitis with or without an associated short bowel syndrome may one day be amenable to transplantation. Major advances in cardiac

and liver transplantation have been made in recent years. Further refinements in immunologic therapy should be followed by successes in gastrointestinal transplantation.

In the longer term, we still await studies defining the etiology of ulcerative colitis and Crohn's disease. An understanding of the underlying causes of these enigmatic diseases will be the first step to a medical cure, perhaps a drug or prophylactic vaccine, at which time surgery may no longer be required.

As physicians, our goal should be earlier diagnosis in severe disease with prevention of abscess, perforation, toxic megacolon, and cancer. Surgery should be carried out before the development of major complications and should be regarded as an extension, rather than a failure of medical therapy. With the possibility of pelvic reconstructive surgery and stricturoplasty for Crohn's disease, earlier surgery can be carried out with less trauma to the patient, less long-term morbidity, and excellent long-term prospects.

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PRESENT TRENDS IN THE TREATMENT OF ULCERATIVE COLITIS

Nonspecific ulcerative colitis as a clinical entity is now well understood. While its etiology remains unknown, its clinical forms, as localized proctitis, as universal or left-sided colitis, or as segmental or right-sided colitis, are readily recognizable. The acute toxic or fulminating form of the disease with its high mortality is also only too well identifiable.

In recent years the therapy—as we call our more or less haphazard attempts at a direct attack on the pathologic process—has undergone and continues rapidly to undergo various changes of mood and of methods. With the introduction of the newer antibiotics and nonabsorbable sulfa preparations, we approach what would seem to be a direct bacteriostasis of or control of the supposedly infectious element. With the suggestion of a psychosomatic etiologic nature of the disease a new problem and a suggested solution seem to be at hand. The indications for surgical treatment are as uncertain as ever, and yet the remarkable success and the relatively greater safety of modern surgical procedures threatens to displace the slower, more uncertain, and often less promising of the plodding medical therapeuses.

In these rapidly changing times and conditions an up-to-date review and an unbiased assay of the methods and results of modern therapy of ulcerative colitis seem well advised. Perhaps after such a review we shall say that light is discernible; perhaps at the end we may be forced to concede that much is still to be desired, that time and nature are still our best and most reliable therapeutic agencies.

B. B. CROHN, MD; H. YARNIS, MD
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Pneumatoceles

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A pneumatocele is a "thin-walled, gas-filled space within the lung, usually occurring in association with acute pneumonia (most commonly of staphylococcal origin) and almost invariably transient...and is usually associated with, and adjacent to, a zone of resolving pulmonary consolidation."¹ Commonly seen as a sequela of staphylococcal pneumonia in infants and young children, pneumatoceles are infrequently seen in adults.^{2,3} Though at one time considered virtually diagnostic of staphylococcal pneumonia, they have been described in pneumonias of other etiology, including *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Hemophilus influenzae*, *Escherichia coli*, *Mycobacterium tuberculosis*, *Proteus mirabilis*, *Pseudomonas*, group A streptococci, *Pneumocystis carinii*, and viral and hydrocarbon induced pneumonia.^{2,4-10}

Pneumatoceles can generally be readily differentiated from lung abscesses by their tendency to change in appearance, size, and location rapidly. They usually resolve within weeks to months. Although usually asymptomatic, they can enlarge and compress the adjacent lung and mediastinum resulting in cardiorespiratory insufficiency; spontaneous pneumothorax may also occur.²

CASE REPORT

A 38-year-old Hispanic woman was admitted to the hospital with a three-week history of progressive weakness, bilateral flank pain, dysphagia, and weight loss, and a one-week history of fever and nonproductive cough. The patient was known to be seropositive for the human immunodeficiency virus (HIV) for three years but did not have clinical acquired immunodeficiency syndrome (AIDS); her risk factor was sexual

contact with an intravenous drug abuser. Her medical history was otherwise unremarkable except for asthma for several years which had not required medical attention, and for *herpes zoster* infection in 1987.

On presentation, the patient was found to be febrile with a temperature of 104°F. Physical examination was significant for orthostatic hypotension, oral candidiasis, shoddy cervical lymphadenopathy, scattered inspiratory and expiratory wheezing bilaterally over the lower lung fields, and bilateral flank tenderness. The chest radiograph demonstrated a right upper lobe infiltrate in addition to diffuse bilateral increased interstitial markings (Fig 1). Laboratory studies revealed normal serum chemistries; white blood cell count, $9.8 \times 10^3/\mu\text{L}$; hemoglobin, 10 g/dL, platelet count, $726 \times 10^3/\mu\text{L}$. An arterial blood gas done while the patient was breathing room air showed a pH of 7.49; PCO_2 , 26 mm Hg; and PO_2 , 80 mm Hg.

Initial therapy included intravenous erythromycin (500 mg every six hours), fluid replacement (normal saline at 125 cc/hr), and nystatin (5 cc five times daily) for the oral candidiasis. The patient remained febrile and although her condition appeared to improve, a repeat chest film on the second day of her hospital stay revealed increased interstitial markings with areas of confluence in the right upper and left lower lung fields (Fig 2). The sputum induced for *Pneumocystis carinii* was reported as positive, whereas all other cultures and sputum stains for acid-fast bacilli were negative. Pentamidine (4 mg/kg per day) was started

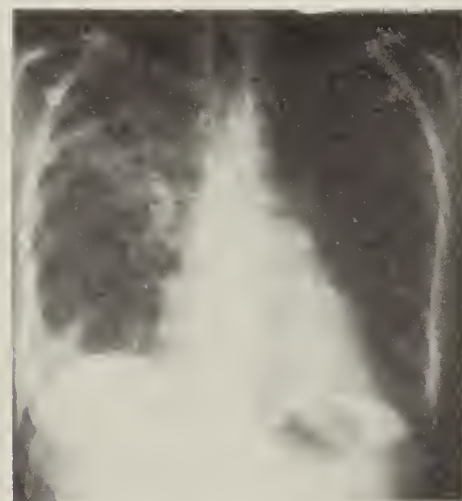


FIGURE 2. Chest film taken on the second hospital day.

via aerosol but was changed to intravenous administration on the fourth hospital day due to progressive dyspnea, worsening interstitial infiltrates on chest film, and deteriorating oxygen saturation.

A small pneumatocele in the right upper lung field was first noted at this time; it was approximately 2 cm in diameter. In retrospect, a pneumatocele was felt to have been present on the patient's previous chest film (Fig 2), though slightly smaller in size. On the sixth hospital day, a repeat chest film showed marked enlargement of the pneumatocele to approximately 8 cm (Fig 3). Given the potential for the pneumatocele to rupture, the patient was transferred to the intensive care area for closer observation. That evening, acute shortness of breath developed with decreased breath sounds on the right side, deviation of the trachea to the left, and decreased oxygen saturation as measured by pulse oximetry. A 16-gauge angiocath was inserted into the right second intercostal space, resulting in a release of air under pressure from the chest and marked improvement in the patient's symptoms and in oxygenation. A chest tube was subsequently placed and maintained due to a persistent air leak.

The chest tube was removed after nine days with complete resolution of the pneumothorax, but with a persistent pneumatocele seen in the right mid-lung field. The patient completed a three-week course of therapy for *Pneumocystis carinii* pneumonia and was discharged on hospital day



FIGURE 1. Chest film taken on admission.

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FIGURE 3. Left, posteroanterior and, Right, lateral chest films taken on the sixth hospital day.

number 26. The last chest film taken prior to discharge showed a persistent pneumatocele.

DISCUSSION

Pneumocystis carinii was first clearly recognized as a human pathogen only relatively recently when it occurred in epidemic form in post-World War II European nurseries, and in sporadic form in the United States in patients with congenital or acquired immunologic defects. The disease subsequently assumed increasing importance with the use of aggressive chemotherapy and immunosuppressive agents in patients with reticuloendothelial neoplasms or organ transplants. Most recently, *Pneumocystis* has become widely recognized as a common and serious opportunistic infection in patients with AIDS.

In the pre-AIDS literature, the usual radiographic appearance of *Pneumocystis carinii* pneumonia (PCP) was generally described as a bilateral interstitial or alveolar pattern, which can

evolve from a primarily perihilar location into a more extensive and diffuse process. Atypical or unusual radiographic appearances of PCP have included reports of lobar distribution, sparing of previously irradiated areas of lung, pleural effusion, pseudonodular pattern, unilateral predominance, cavitation and necrosis, pulmonary nodules, pneumothorax, a normal chest film, and possibly intrathoracic adenopathy.¹¹⁻¹⁵ In spite of numerous papers on this topic, only one pediatric case report describes the occurrence of pneumatoceles that developed after the institution of mechanical ventilation for respiratory failure.¹⁰

Various authors have similarly reported on the radiographic manifestations of PCP in AIDS patients and have noted the same spectrum of findings.¹⁶⁻²¹ However, compared to the paucity of cases with pneumatocele formation in the non-AIDS or early AIDS literature, there have been several recent reports documenting the presence of pneumatoceles in patients with AIDS and PCP.²¹⁻²⁴ Although still a relatively infrequent finding, it appears that pneumatocele formation may be becoming a more common sequela of PCP in patients with AIDS. This is of particular interest given the prior consensus that pneumatocele formation was uncommon in the adult compared to the pediatric population in other types of pneumonia.

The precise mechanism underlying the formation of pneumatoceles is not known. Caffey²⁵ proposed that pneumatoceles are caused by localized pulmonary emphysema distal to a transient bronchial obstruction of a check valve type, and that the cystic dilations lie within the pulmonary tissues. He also postulated that extra-alveolar collections of air in the form of subpleural blebs may be present and may coexist with the intraparenchymal collections of air. The extra-alveolar collections could result from the rupture of alveolar walls with extravasation of air into the interstitial spaces. Subsequently, Conway,²⁶ although generally concurring with Caffey as to the mechanism by which pneumatoceles are produced, also speculated that perforation or ulceration of small bronchi or alveoli may occur, which would allow air to enter the tissues.

Boisset, in 1972,⁸ presented anatomic evidence to refute Caffey's and Conway's postulate concerning intraparenchymal pneumatoceles, and to support the contention that the term "sub-

pleural emphysema" should replace the term pneumatocele. He presented pathologic evidence that ruptured bronchiolar walls allowed communication between the bronchiolar lumen and the interstitial space, thereby establishing an anatomic point at which air could escape into the interstitium. Air in the interlobular septa thus establishes "air corridors" through which air could reach the subpleural connective tissue and establish subpleural collections of air. Quigley et al²⁷ later presented pathologic evidence to support the intraparenchymal nature of pneumatoceles. He postulated that the underlying mechanism was a combination of parenchymal necrosis and check valve bronchiolar obstruction.

The precise pathogenesis of pneumatoceles may never be fully elucidated. Pathologic specimens are generally not available for study due to the generally benign clinical course of pneumatoceles. Even when specimens are available, their examination may not add insight to the physiologic or mechanical forces that dictated the formation of pneumatoceles in vivo, as those forces are no longer present and can not always be reproduced. Difficulties in preparing specimens for pathologic review may also introduce a degree of artifact into the analyses. Finally, different underlying etiologies may offer seemingly contradictory evidence as to the mechanism for pneumatocele formation; some cases may demonstrate necrosis, which is due to the primary cause and is not part of the pneumatocele per se. In all likelihood, as Conway originally suggested, there may be a product of mechanical (ie, a check valve obstruction) and inflammatory forces operating in the development of pneumatoceles, and the relative contribution of these forces could vary in different disease states.

The concept of pulmonary interstitial emphysema (PIE), which is receiving increased attention due to heightened interest in the respiratory distress syndrome, may represent a unifying theory to encompass these seemingly contradictory postulates and observations. PIE is felt to represent the presence of air within the connective tissue of the perivascular and interlobular septa. It develops along the interlobular septa following the overdistension and rupture of the alveolar base, the segment of an alveolus directly contiguous to the fluid rich tissue surrounding the blood vessel. This allows air to leak into the septal connective tissue. Air can then remain localized or can dissect central-

ly along vessels to the mediastinum or peripherally to and through the pleura to cause a pneumothorax.²⁸ Radiographic findings of PIE include small parenchymal cysts, linear streaks of air radiating toward the hilum, perivascular air surrounding large pulmonary vessels projected end-on to produce perivascular halos, intraseptal air collections surrounding small perihilar vessels producing a pattern of small dots surrounded by areas of radiolucency, pneumatoceles (large parenchymal cysts), and collections of air along the visceral pleural surface manifested by blebs or lucent lines. Complications of PIE can include pneumothorax or pneumomediastinum²⁹ as well as pneumopericardium, pneumoperitoneum, and subcutaneous emphysema.³⁰

The physiologic conditions predisposing to the development of PIE include local or diffuse overinflation of the alveoli, decreased blood flow through the pulmonary vessels, and increased intra-alveolar pressure. These conditions, which can exist independently or in combination, create an increased pressure gradient between the alveoli and perivascular sheath leading to rupture of the alveolar base and leakage of air into the interstitium. Coughing, starting at a high lung volume and generating high airway pressures, and positive pressure ventilation are common clinical causes of PIE.^{29,30} The concept of PIE presumes some disruption of the alveolus with extra-alveolar accumulation of air. In some cases a check-valve mechanism must exist as well, in order to account for the development of tension pneumothorax or large pneumatoceles with compression of adjacent lung parenchyma.³⁰

PIE is an interesting concept in that it offers a single mechanism to account for the occurrence of both pneumatoceles and pneumothoraces, which have also been noted to occur with increasing frequency in patients with PCP and AIDS.³¹ The concurrent presence of pneumatoceles and pneumothorax, as seen in this case, would imply that a single pathophysiologic mechanism may underlie both phenomena. Only one previous author has noted the simultaneous presence of pneumatoceles and a pneumothorax in a patient with AIDS and PCP.³¹ Although theoretically a pneumothorax could result from rupture of a pneumatocele, both the frequency of cases noting one or the other finding, as well as the persistence of the pneumatocele in the case presented here after the development of a pneu-

mothorax, would support the ability of these conditions to develop independently. Other authors have noted the presence of subpleural deposits of organisms as an explanation for recurrent spontaneous pneumothoraces in patients with PCP or staphylococcal endocarditis.^{32,33} Whereas this may represent an alternative process in some cases of pneumothorax, it does not negate a mechanism consistent with PIE.

An additional question that needs to be addressed is why there should be an apparent increase in the frequency of pneumatocele formation in patients with AIDS and PCP compared to prior populations. One explanation could be that the increase is more perceived than real and simply represents an increased interest in PCP secondary to the current epidemic and increased reporting. Presuming, however, that this is a real phenomenon, what are some of the possible explanations?

The clinical characteristics of patients with AIDS presenting with PCP could be a predisposing factor to the development of PIE, and subsequently either pneumatoceles or pneumothoraces. These include the relative chronicity of symptoms prior to admission as well as the prevalence and severity of cough. Although being present in the majority of cases, cough was not felt to be an outstanding feature and was frequently absent in immunosuppressed patients without AIDS and pediatric cases with PCP.^{34,35} The severity as well as the duration of cough in patients with PCP and AIDS may be a factor in their increased risk for the development of PIE, and pneumatoceles or pneumothorax, as was previously discussed.

Although there does not appear to be a significant degree of tissue necrosis in PCP which could contribute to the alveolar rupture, Eng et al²³ has postulated that the chronicity of the disease process would allow for an increase in the number of activated macrophages, which are known to produce elastase. This could play a role in altering the alveolar wall integrity and predispose to the rupture that is postulated to occur with PIE. The abundant intra-alveolar exudate, *Pneumocystis* organisms, and connective tissue proliferation could conceivably act as a check valve in causing an obstruction as well. Additionally, the underlying immune defect in AIDS, or infection with the human immunodeficiency virus itself, may alter the lung's response to the *Pneumocystis* organisms.

Obviously, mechanical ventilation could be a contributing factor, but this case, as well as prior reports, amply demonstrate that both pneumatoceles and pneumothoraces can occur in spontaneously breathing patients with PCP and AIDS. Although the underlying pathophysiology may be pulmonary interstitial emphysema, pathologic "proof" is not available. The increased frequency of both pneumatoceles and pneumothoraces is of concern, as they may significantly contribute to both the morbidity and mortality associated with this particular opportunistic infection in patients with AIDS. Although the clinical course of pneumatoceles is generally benign, in patients with serious impairment of ventilatory reserve a large and/or expanding pneumatocele could precipitate respiratory failure.

More information is required to define further the biologic response of the lung to PCP as well as to delineate any predisposing factors to the development of either pneumatoceles or pneumothoraces. In the interim, patients with PCP should be monitored for the development of radiographic changes consistent with PIE, and they should be followed closely. Perhaps symptom intervention (ie, cough suppression) or earlier recognition and treatment may reduce the frequency of these complications.

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Traumatic thrombosis of a vertebral artery in a hypoplastic vertebrobasilar system

Protective effect of collateral circulation

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Dissection and thrombosis of a vertebral artery may follow blunt craniocervical trauma. When one vertebral artery is occluded, its counterpart will continue to supply the basilar circulation. Propagation of thrombus from the occluded vertebral artery into the basilar artery may occur, and anticoagulation therapy is indicated to prevent catastrophic basilar thrombosis. We report on a patient with symptoms of vertebrobasilar ischemia after neck trauma, who was found to have thrombotic occlusion of a hypoplastic vertebral artery. His right vertebral artery was also hypoplastic, and we infer that he did not incur major neurologic impairment because his brainstem and cerebellum had an unusual collateral blood supply.

CASE REPORT

A healthy 45-year-old mechanic tripped and fell down a flight of stairs at home, striking

the back of his neck against a stair. He did not lose consciousness and did not report any external signs of trauma.

Over the next few days, he experienced a dull ache at the nape of his neck, and a week after the fall he experienced a few seconds of vertical diplopia. During the next three weeks, he had approximately 25 similarly brief episodes of vertical diplopia present in all fields of gaze, accompanied on several occasions by dizziness, on one occasion by right facial numbness, and on another by paresthesias of the right hand. When he was examined four weeks after the fall, no neurologic abnormalities were found. Magnetic resonance imaging (MRI) of the posterior cranial fossa, echocardiography, electroencephalography, and brainstem auditory evoked potentials were all within normal limits.

Since the clinical history suggested vertebral artery dissection, cerebral angiography was performed. Bilaterally hypoplastic vertebral arteries and a compensatory pattern of circulation were seen, as shown schematically in Fig 1. The third portion of the left vertebral artery was occluded by thrombus (Fig 2); the fourth portion of the left vertebral artery and both posterior inferior cerebellar arteries filled by flow from the right vertebral artery (Fig 3); the basilar and anterior inferior cerebellar arteries filled during the internal carotid injection (Fig 4).

When treatment was initiated with hepa-

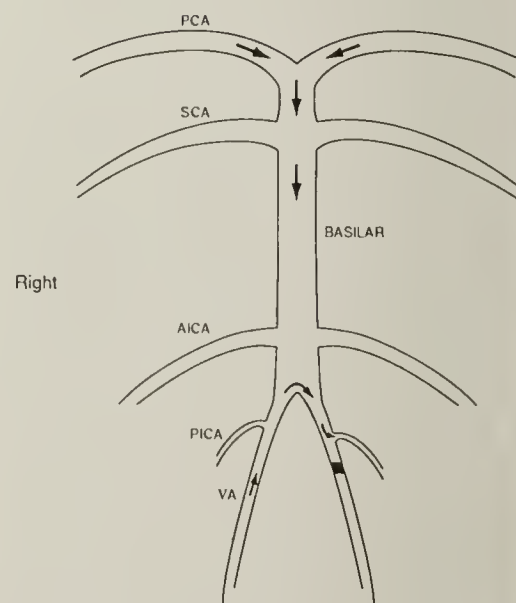


FIGURE 1. Schematic diagram of vertebrobasilar circulation. PCA, posterior cerebral artery; SCA, superior cerebellar artery; AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery; VA, vertebral artery.

rin followed by warfarin, the patient became asymptomatic. No further vertebrobasilar ischemic events were experienced for six months. Then the patient reported one episode in which his legs transiently gave way without loss of consciousness. At that time, the prothrombin time was 16.2 seconds. Af-

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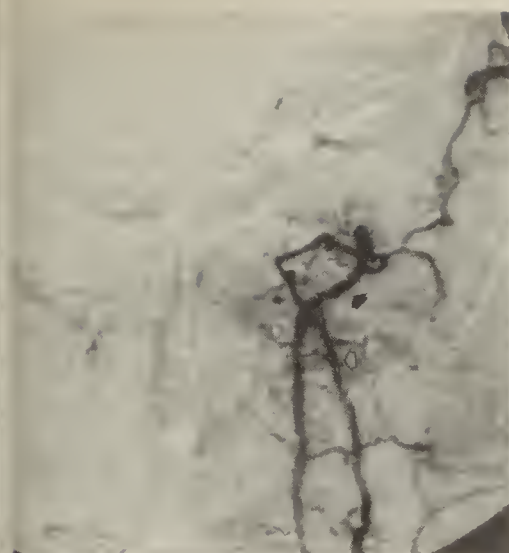


FIGURE 2. Cerebral angiogram after injection into left vertebral artery (solid arrow) shows occlusion of third portion of left vertebral artery, and collateral vessel (open arrow).

ter adjustment of the dosage of warfarin to maintain the prothrombin time above 18 seconds, he again became asymptomatic. Selective angiography of the left vertebral artery nine months later still showed obstruction of the third portion of the left vertebral artery.

DISCUSSION

Vertebral artery dissection, occlusion, or aneurysm may result from various forms of trauma to the head and neck.¹ Even minor trauma may be sufficient, including chiropractic manipulation, yoga exercises, calisthenics, archery, swimming, or ceiling painting.² The most common site of injury to a vertebral artery is the third portion, where the vessel is subject to extrinsic compression as it passes from the atlas to the foramen magnum.³ After injury to a vertebral artery, occipital headache



FIGURE 3. Cerebral angiogram after injection of right vertebral artery shows filling of left posterior inferior cerebellar artery (open arrow), and occluded portion of left vertebral artery (solid arrow).

and neck pain may be followed by neurologic sequelae ranging in severity from transient ischemic attacks to fatal brainstem or cerebellar infarction. Although the paired vertebral arteries carry only 10% of total blood flow to the brain, they supply structures vital to consciousness, respiration, circulation, and integrated motor and sensory functions.⁴

This patient experienced only transient symptoms of brainstem ischemia despite occlusion of one of two hypoplastic vertebral arteries. Even in patients without congenital defects of the circle of Willis, traumatic unilateral vertebral artery thrombosis may not produce any permanent neurologic sequelae, particularly if the nondominant vertebral artery is involved. Congenital defects of the circle of Willis are common and often occur in conjunction

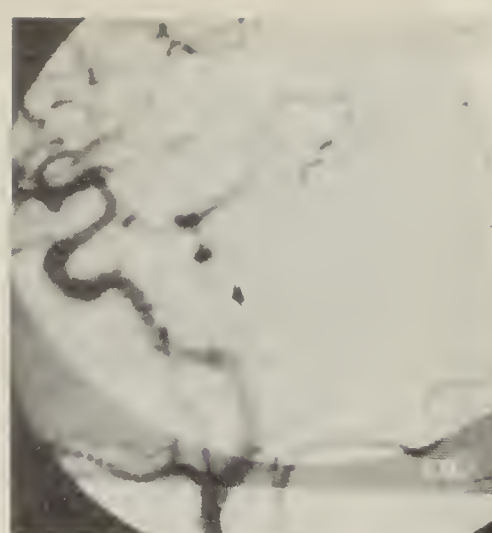


FIGURE 4. Cerebral angiogram after carotid injection shows retrograde filling of basilar artery (solid arrow).

with the establishment of a collateral circulation. These alternative arterial pathways, particularly the potential supply from the external carotid through the occipital branches, play an important part in the circulation of the posterior fossa. In this patient, an effective collateral circulation maintained perfusion of the vertebrobasilar territory. His ischemic symptoms terminated with anticoagulation therapy, which may have provided further benefit by preventing propagation of the vertebral thrombus into the basilar artery.

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Left paraduodenal hernia

LEO PATRICK SULLIVAN, MD; PAUL G. DAVIDSON, MD; LEONARD F. BERLINER, MD

Internal abdominal hernias are a relatively uncommon cause of abdominal pain, accounting for less than 1% of bowel obstructions. About half of these are paraduodenal hernias. Most para-

duodenal hernias are found at laparotomy or autopsy. They are generally considered in the differential diagnosis of small bowel obstruction when no previous abdominal surgery has occurred. It is perhaps not well known that the radiographic findings of this entity on upper gastrointestinal series with small bowel follow-through are sufficiently characteristic to make a definitive diagnosis prior to surgery.

In this report, the characteristic findings of a left paraduodenal hernia on small bowel series are well demonstrated. In addition, the embryologic basis and surgical management of this condition are reviewed.

CASE REPORT

A 25-year-old man with no remarkable past medical history and no previous surgery presented to the Staten Island University

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FIGURE 1. Upper gastrointestinal series with small bowel follow-through clearly demonstrates displacement of the small bowel to the left upper quadrant of the abdomen. The finding is consistent with a left paraduodenal hernia.



FIGURE 2. The small bowel, now reduced from the hernia sac, is seen to have a more normal distribution in the peritoneal cavity.

Hospital with a four-month history of recurrent postprandial abdominal pain and bloating. The pain usually occurred 30 to 60 minutes after a large meal and was relieved by lying supine for about 30 minutes. The patient denied any fever, chills, jaundice, change in bowel habits, or weight loss. He came to the emergency room during his latest episode of abdominal pain, since it had not resolved after lying supine for two hours.

Physical examination revealed a young man with a muscular body who was in mild distress. The abdomen was distended with high-pitched bowel sounds. There was no palpable abdominal mass and no hernia was present. Rectal examination was negative for a mass or occult blood.

The results of laboratory tests, including a leukocyte count of 7,000/dL, were within normal limits. The patient's symptoms completely resolved approximately 30 minutes after being examined. His abdomen became soft and was no longer tender. Plain abdominal films were normal at this time. The patient was admitted for observation and further evaluation.

A barium study of the upper gastrointestinal tract, including small bowel follow-through was performed. The study initially demonstrated displacement of the small bowel to the left side of the abdomen, consistent with a left paraduodenal hernia (Fig 1). At this point in the examination, the patient experienced his usual abdominal symptomatology. Follow-up films a short time later, and after the patient's abdominal pain had resolved, showed resolution of the obstruction and a more normal distribution of bowel loops (Fig 2).

Since the patient had suffered several epi-

sodes of obstruction in the past it was felt that surgical correction was indicated to reduce the risk of incarceration or strangulation. The patient underwent standard bowel preparation for surgery and was brought to the operating room. At laparotomy, all but the last 30 cm of ileum was found in the hernia sac. The left kidney could not be found during exploration of the abdomen and pelvis. The hernia contents were easily reduced. The anterior wall of the sac was excised from the left of the inferior mesenteric vein up to the descending colon. Then the duodenojejunal flexure was moved to the right and fixed with interrupted sutures of 00 silk. The duodenojejunal flexure was placed over the inferior mesenteric vein. The patient has been asymptomatic during follow-up over the past two years.

DISCUSSION

Internal hernias are a rare cause of small bowel obstruction, present in less than 1% of cases. Paraduodenal hernias comprise 53% of internal hernias and occur three times more commonly on the left side than on the right.¹ Rarely they are found beneath the transverse mesocolon.² This type of hernia is actually a congenital malrotation of the gut, which can be better understood after a discussion of the pertinent embryology.

By the fourth or fifth week of normal fetal development, the midgut lies outside of the abdominal cavity in the umbilical sac.¹ The vitelline duct divides the midgut into the prearterial or cephalad segment and the postarterial or

caudad segment. The prearterial segment forms the jejunum and most of the ileum. The post-arterial segment forms the terminal ileum, cecum, ascending colon, and the right half of the transverse colon.² As the midgut elongates, it rotates 90° counterclockwise about the superior mesenteric artery. By the tenth week of fetal development, the peritoneal cavity has reached a size that is capable of accommodating the entire gut. As it returns to the abdomen, the bowel rotates an additional 180° in a counterclockwise direction. The right colon passes over the small intestine and becomes fixed in its normal position along the right side. The mesocolon on the left and right sides, and the mesentery of the duodenum fuse with the peritoneum of the posterior abdominal wall. If fusion does not take place, a potential space is created into which small bowel may herniate.³

In a left paraduodenal hernia, the small bowel invaginates through an unsupported area of the mesentery of the left colon. The term paraduodenal hernia is therefore actually a misnomer and is better termed mesocolic. The vascular margin of this area is the inferior mesenteric vein and the left colic artery.³

Authors differ in their opinions concerning the optimal surgical repair. Bartlett et al³ advocate division of the mesenteric vessels to obliterate the hernia sac and allow restoration of normal enteric anatomy. They reported no complications in using this technique with two patients. Most other authors prefer not to divide the mesenteric vessels. The type of repair presented here has previously been described by Davis.⁴ With this approach, meticulous dissection is used to spare the inferior mesenteric vein and left colic artery while avoiding injury to the marginal artery of Drummond.

Most paraduodenal hernias are found at laparotomy or autopsy. Typically, the surgeon does not have the benefit of preoperative radiologic studies. When the diagnosis is suspected in an elective situation, preoperative work-up should include a small bowel follow-through. However, the study may be normal when the patient is asymptomatic.

The small bowel follow-through series in this case report clearly demonstrates the features of a left paraduodenal hernia. Multiple loops of small bowel may be seen in a circumscribed sac on the left side of the abdomen (Fig 1). The efferent loop (in this example,

terminal ileum) may be seen exiting from the hernial orifice, marked by an abrupt change in caliber. Loops of small bowel could be seen intermittently traversing the hernia orifice during fluoroscopic examination. Meyers⁵ showed that superior mesenteric artery angiography will reveal a reversal of the path of the jejunal arteries. A line connecting these points represents the anterior surface of the neck of the hernia sac.

There are anecdotal reports in the literature of computerized tomography (CT) demonstrating a paraduodenal hernia.^{6,7} CT may reveal a loop of bowel in the hernia sac, which is posterior to the pancreas.

Also of interest in this case is the absence of the left kidney, discovered on CT imaging of the abdomen and pelvis. The scan was performed coincidentally, as part of a prospective study underway at this institution. There is one reported

case in the literature of a paraduodenal hernia being associated with renal displacement.⁸ This is the first reported case of a paraduodenal hernia being associated with ipsilateral renal agenesis. The significance of this association is not understood.

Most authorities agree that a left paraduodenal hernia is caused by invagination of small bowel through an unsupported area of the descending mesocolon between the fourth and tenth week of fetal life, when development of the kidney is also taking place. If the hernia is large enough, one might speculate that it might prevent cranial migration of the ureteric bud toward the metanephric cap. Proliferation of the metanephric cap would not occur and the kidney would not develop. However, as the incidence of unilateral renal agencies is 1 of 1,500 live births,⁹ and there are more than 1,400 cases of paraduodenal hernia reported in the lit-

erature, the association may only be coincidental.

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Increased lead absorption in a potter and her family members

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Effects on health of exposure to inorganic lead are not unusual findings in today's occupational and environmental medicine practice. Although the acute manifestations of lead poisoning are rarely encountered among workers because of recent improvements in protective industrial hygienic measures and stricter regulations, significant lead exposure may still occur among employees of certain high-risk occupations.¹ Concern over potentially adverse effects on children and their development has spurred much debate and has been an important consideration in the promulgation of a new lead standard for ambient air in the United States.²⁻⁴

Artists such as potters belong to an

occupational group that traditionally has been associated with increased risk for lead poisoning. Their lead-containing glazes are a known source of increased lead absorption. Because of an awareness of this risk, lead frits were developed during the early part of this century in Great Britain. In the fritted lead glazes, the metal is bonded into the constituents of the glaze and is thereby much less soluble. This results in a significant reduction in hazardous exposure to those manufacturing lead-glazed pottery items and those using them. Lead frits are widely considered as "safe" compounds because of the often incorrect assumption that the fritted lead is insoluble. Consequently, there has been a tendency among artists over the years to reduce levels of respiratory protection.⁵

Following is the description of an artist and her family who experienced adverse effects resulting from their work with lead frits and other glazes.

CASE REPORT

The patient was a 35-year-old woman who had worked as a potter for 17 years. She

sought medical attention from us for two reasons. She had read an article in a weekly magazine that reported on an unusual case of lead poisoning in an art conservator, who had been evaluated by us. (The article referred to a case report, which we had published in a medical journal.)⁶ In addition, she had noticed a labeling change on one of the products she had used for a long time, now mentioning a potential lead hazard.

The patient reported using an air brush when applying glazes containing fritted lead onto ceramic tiles. On pottery, she routinely used nonfritted lead glazes, which she mixed herself with kaolin (clay). She devoted approximately 20 hours per week to the tile work, and she described an air mist that was present when applying the glaze. There was also frequent skin contact with the glaze material. She reported using an Occupational Safety and Health Administration (OSHA) approved respirator (face mask) as protection against airborne contaminants. In addition to lead-containing materials, she also frequently handled silica compounds and various oxides of metals as stains.

Her studio was approximately 600 square feet and occupied half the surface of a floor in a loft. The other half served as the family's living quarters. The studio was separated from the apartment by a corridor and an opening with a plastic curtain. The patient

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reported taping the plastic curtain when firing the kiln in order to achieve better separation between the living quarters and the studio.

The patient's five-year-old daughter was often present in the studio while she was working, especially during a five-month period preceding the medical examination. The little girl used to touch the glaze and to paint her own pottery and wore only a paper face mask. Prior to that, between the age of five months and three years, she had only passed through the studio occasionally. The patient's husband was engaged in another occupation, with no known lead exposure, but during a five-month period preceding the examination, he had assisted with the removal of large and heavy objects from the kiln.

Her medical history was noncontributory. She reported no specific gastrointestinal symptoms, but fatigue was a prominent symptom. However, the patient associated this symptom with her long work hours. She reported no sleep disturbances but had experienced slight dizziness. However, this symptom did not cause her to seek medical attention. The physical examination was normal at this presentation. No Burtonian gum lead line was observed; the blood pressure was 120/75 mm Hg; and the pulse was 72/min and regular. The neurologic examination was normal with no obvious weakness of the extensor muscles. A complete blood count was also normal.

The daughter did not report any symptoms, such as malaise, headache, or abdominal cramps. There were no noted behavioral changes, and she was functioning well in kindergarten. A routine pediatric evaluation four months prior to this presentation was normal. Her examination at this time revealed a cheerful, cooperative child with an entirely normal physical and neurologic evaluation. A complete blood count did not reveal any abnormalities.

Blood lead concentrations were measured by atomic absorption spectrophotometry. Erythrocyte protoporphyrin (EP) levels were determined according to the method of Sassa et al.,⁷ and the activity of delta-aminolevulinic acid dehydratase (ALA-D) was measured according to the method of Granick et al.⁸ The ratio between ALA-D activated by dithiothreitol and nonactivated ALA-D was used to express the impact of the lead-related effect on the enzyme. The laboratory findings evaluating lead absorption and lead-related biochemical effects are summarized in Fig 1.

The artist and her daughter manifested significantly elevated blood lead concentrations at the initial examination—48 mcg/dL (2.32 mmol/L) and 54 mcg/dL (2.61 mmol/L), respectively. The husband's blood lead concentration was at an acceptable level. The EP levels were elevated in the artist and her daughter, whereas the husband's EP concentration was within normal limits. However, all three family members manifested abnormal activity of ALA-D, indicating a lead-associated effect. At that

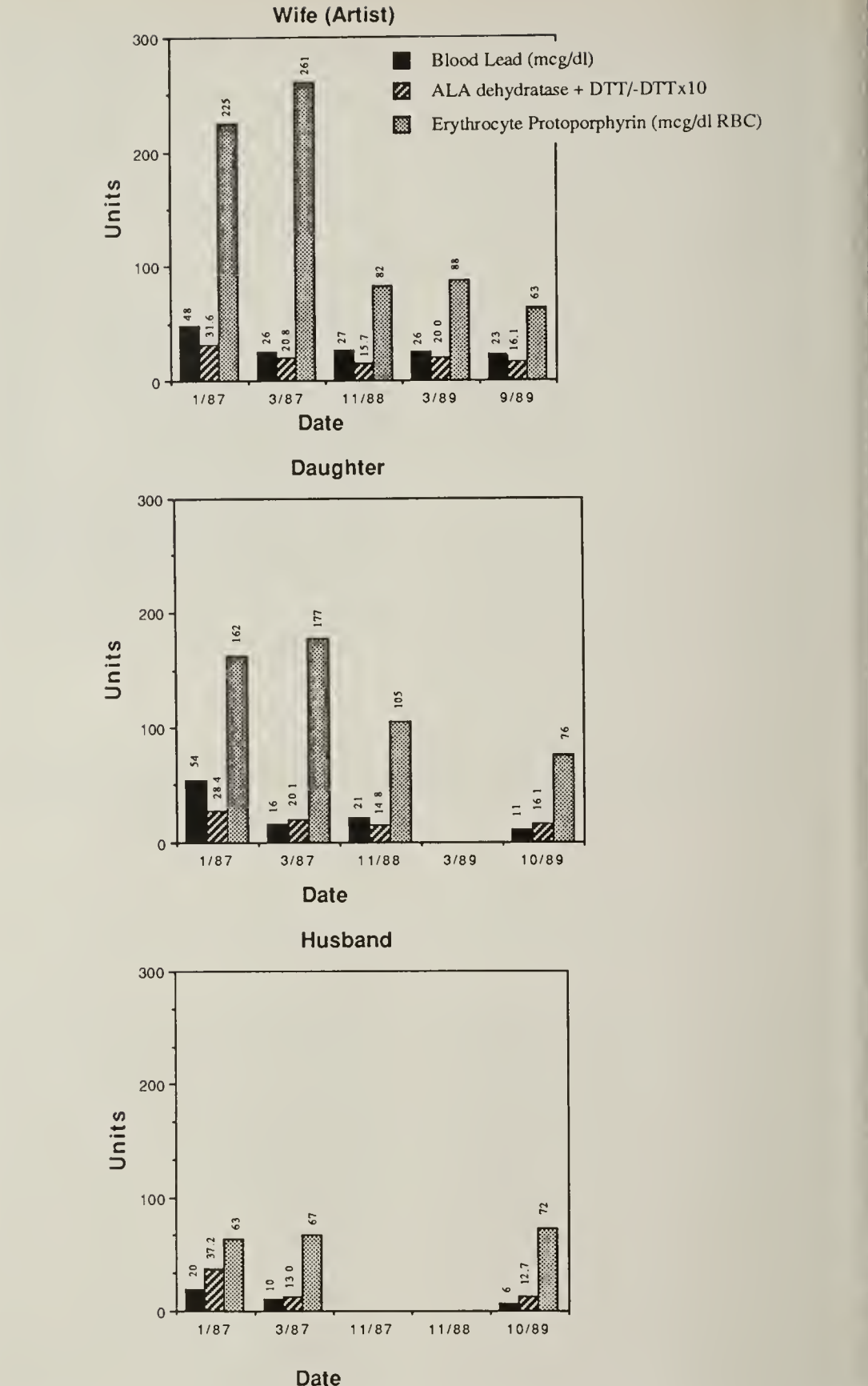


FIGURE 1. Blood concentration, erythrocyte protoporphyrin level and ALA-D activity of artist and family members at initial examination and subsequent follow-up visits. Laboratory reference values: Blood lead (mcg/dL), action level in children is 25 (1.21 mmol/L); Occupational Safety and Health Administration blood lead standard is 40 (1.93 mmol/L); ALA-D ratio, mean $\pm$ SD = 2.16 $\pm$ 0.69, n = 15; erythrocyte protoporphyrin (mcg/dL RBC), adult male: mean $\pm$ SD = 56.1 $\pm$ 15.6, n = 66; adult female: mean $\pm$ SD = 66.6 $\pm$ 20.4, n = 94; children: mean $\pm$ SD = 81.3 $\pm$ 33.3, n = 61.

time, all were asked to discontinue potential exposure to lead in the described occupational setting.

Six weeks later, improvements were noted in blood lead and ALA-D activity; the latter had become normal in the husband, whereas the mother and daughter still showed abnormalities in this parameter. No significant changes had occurred in EP levels. Some 21

months after the initial examination, ALA-D activity and EP concentrations were within normal limits despite continued work with extreme precautions and the phasing out of all lead-containing compounds. The blood lead concentrations were still slightly elevated when compared with blood lead levels found in persons with no history of a specific source of lead exposure, except for exposure

experienced in the general environment. However, the patient's blood lead levels were within a range that did not result in biochemical abnormalities in ALA-D activity or EP concentration. Prolonged follow-up demonstrated a complete return to normal of all variables, except for a blood lead concentration of 23 mcg/dL (1.11 mmol/L) in the artist herself. Again, the biochemical indicators of lead intoxication were normal.

DISCUSSION

This report describes an experienced artist-potter, who, in spite of the primary use of fritted lead glazes (but with some limited use of nonfritted glazes), was diagnosed with an elevated blood lead level and other abnormal biochemical signs of lead intoxication.

In spite of the artist's great awareness of the potential hazard and her taking rigorous protective measures, the blood lead concentrations remained slightly elevated for a long time after discontinuation of the original exposure. The ALA-D activity came into an acceptable range following discontinuation of the exposure and remained normal throughout the 22-month period of observation. It is possible that very low-level exposure to lead occurred during some period of this time, since one of the materials used during the spring and summer of 1989 and thought to have been lead-free contained "traces of lead." However, the impact of several years of exposure may have also contributed to the slightly elevated blood lead levels. These were low enough not to cause noticeable abnormalities in the heme synthesis. This is particularly apparent by the normalization of the ALA-D activity, which is the most sensitive heme-related parameter available in the assessment of lead-induced effects.

Of additional interest and concern was the finding of increased lead absorption in the artist's five-year-old daughter and in her husband. Both were often present in the studio when work was in progress. The child, on occasions, also performed her own work, handling lead frits and painting pottery items, and she was at risk for both indi-

rect (bystander's) and direct occupational exposure. She manifested elevated blood lead concentrations and abnormal protoporphyrin levels, as well as an inhibition of ALA-D. The husband assisted with one particular task—removing heavy art objects from the kiln. That exposure was apparently lower than those experienced by his wife and daughter, since his blood lead concentrations were within acceptable ranges. In spite of this finding, mild inhibition of ALA-D was initially found, suggesting significant exposure.

The long-term follow-up examinations enabled us to identify the exposure source as the handling of lead-containing materials, thus being work related. However, because of the elevated blood and erythrocyte protoporphyrin concentrations in the child, an inspection and environmental evaluation of the premises were performed by the local health department. Painted surfaces were examined with the assistance of an x-ray fluorescence meter (XRF). Although some surfaces, such as window openings and four walls, were covered with paint that contained 0.7 mg of lead or more per square centimeter of surface, there were no signs of teeth or gnaw marks on any of the surfaces to indicate that the child had attempted to ingest paint chips. However, a sample of one of the glazes used by the artist contained 18% lead. The potential lead hazard on the interior surfaces of the domicile abated during a six-month period. Additional industrial hygienic evaluations and air samplings were not carried out.

This case report illustrates that artists who make pottery may handle potentially harmful substances, against which industrial hygienic protective measures are necessary in order to minimize the risk for adverse health effects. The awareness of such risk in this case, made early detection of adverse lead-related effects possible. This was particularly important because of the lead exposure experienced by the artist's child. Special precautions must be taken to prevent small children from being exposed to hazardous materials in the

artist's environment. In this case, exposure was to a material containing lead, to which children are more sensitive than adults. Prolonged exposure under these conditions could have resulted in serious adverse health effects.⁹

Information about the contents of materials and their potential health effects ought to be more widely disseminated among artists working with pottery and ceramics. Their work area should be considered as an industrial environment and must be strictly separated from actual living quarters. Since many art studios are located in the immediate vicinity of the domicile, it is recommended that expert advice be obtained concerning the safety aspects of the art work performed.

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Responsibilities of health yuppies

TO THE EDITOR: In the February 1991 issue of the *New York State Journal of Medicine*, Dr Kavalier¹ describes and deplores the parlous state of society. She then admonishes young physicians, to whom she refers with the pejorative epithet of "health yuppies," to behave properly and charitably, and to practice good medicine. What is the point of this commentary with its blanket preachment and inferred indictment of young doctors?

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1. Kavalier F: Responsibilities of health yuppies. *NY State J Med* 1991; 91:43-44.

Health yuppies' responsibilities

TO THE EDITOR: As a life member of the medical society, I receive and read the *Journal*. Dr Florence Kavalier's commentary, "Responsibilities of health yuppies," was excellent.¹ I fully agree with her evaluation of new medical professionals.

My father practiced medicine in Brooklyn for 60 years and I received good early training from him about how to treat patients and to consider their needs. I graduated from New York University School of Medicine in 1934, and did my surgical residency at Mt Sinai Hospital in New York. Although I retired in 1976, I still receive calls from my former patients. My desire to help people has not diminished and giving advice is now easier without the problems associated with documentation, fees, malpractice insurance, and prescriptions. The *Journal* helps me to keep up with what is new in medicine. After I read it, I donate it to the medical library of the local hospital and I am certain that your article will be read by many. Keep up the good work.

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1. Kavalier F: Responsibilities of health yuppies. *NY State J Med* 1991; 91:43-44.

Requirement that prescriber's name be imprinted or stamped on prescription forms

TO THE EDITOR: A recent appellate court ruling in New York, *Izzo v Manhattan Medical Group, PC*,¹ makes it essential that the prescription form contain the "mechanically" imprinted or stamped name of the prescriber. In 1985, the New York State Legislature amended the law regulating the dispensing of prescription drugs (Education Law, section 6810(a)(8)) by adding a new provision, which states:

Every prescription (whether or not for a controlled substance) written in this state by a person authorized to issue such prescription and containing the prescriber's signature shall, in addition to such signature, be imprinted or stamped legibly and conspicuously with the printed name of the prescriber who has signed the prescription. The imprinted or stamped name of the signing prescriber shall appear in an appropriate location on the prescription form and shall not be entered in or upon any space or line reserved for the prescriber's signature. The imprinted or stamped name shall not be employed as a substitute for, or fulfill any legal requirement otherwise mandating that the prescription be signed by the prescriber.

In addition to the statute, regulations of the New York State Department of Health regarding the prescribing of controlled substances contain similar provisions. Section 80.67 of the department's regulations regarding prescriptions for Schedule II and certain other substances that must be issued on the official New York State prescription form states that the original and both copies must contain:

The printed name, address, registration number, telephone number, and handwritten signature of the prescribing practitioner. The printed name of the prescriber who has signed the prescription, shall appear in an appropriate location on the prescription form and shall not be entered in or upon the space of line reserved for the prescriber's signature. The imprinted or stamped name shall not substitute for or fulfill any legal requirement otherwise mandating that the prescription be signed by the prescriber.

Section 80.69 of the department's regulations regarding prescriptions for Schedule III, IV, and V substances contains the same provision as above.

This statutory requirement was virtually unnoticed until the *Izzo* decision. The case was brought as a wrongful death action by the administratrix of the estate of Frank J. Izzo. The administratrix claimed that the death of the decedent, her husband, was caused by acute drug intoxication brought about by his ingestion of controlled substances. Among the defendants were seven physicians and 12 pharmacies.

One of the defendant pharmacies dispensed Empirin 3 (Empirin with codeine) to the decedent on a union prescription form, which, in addition to the drug prescribed, included the handwritten DEA number, address, and telephone number of a dentist. The form bore the signature of the prescribing dentist which according to the plaintiff the decedent had forged, and the hand-printed name of the dentist. The form did not include the mechanically imprinted name of the prescriber. The decedent had allegedly become physically dependent on drugs, and the autopsy showed that the death of the decedent was caused by a drug overdose. The plaintiff alleged that the pharmacy was negligent for filling an invalid prescription.

The lower court dismissed the case against the pharmacy, holding that the hand-printing of the prescriber's name on the prescription form complied with the statutory requirement of Education Law section 6810(a)(8). On appeal, however, the appellate court reversed, and reinstated the claim against the pharmacy. The appellate court ruled that the statute requires the prescriber's name to be "mechanically" imprinted or stamped along with the prescriber's signature, and that the pharmacy violated the law by filling a prescription which did not have the prescriber's name mechanically imprinted on the form.

Having decided that the pharmacy violated the law, the appellate court

next decided that a violation of Education Law section 6810 creates a private right of action in favor of a person who was injured as a result of an illegally and improperly filled prescription. Left unanswered for now is whether the plaintiff can prove that the filling of the prescription by the pharmacy contributed to the death of the decedent. The ruling in *Izzo* gives the plaintiff the opportunity to prove this claim in court.

The office of General Counsel of the Medical Society of the State of New York has received a number of inquiries from physicians regarding the refusal of pharmacies to fill prescriptions that do not bear the mechanically imprinted or stamped name of the prescriber. Physicians have asked why if Education Law section 6810(a)(8) has been in effect since 1985, pharmacists have only recently refused to accept the hand-printing of the prescriber's name. The expansion of liability to pharmacists (and conceivably physicians) in *Izzo* explains why.

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General Counsel

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1. AD2d, 560 NYS2d 644 (1st Dep't 1990).

Incidence of high-level gentamicin resistance among enterococci isolated from blood cultures in a community hospital in New York

TO THE EDITOR: In light of the recent noted increase in antibiotic resistance among enterococci, we undertook to review the blood culture results from our Microbiology Laboratory for a six-month period. Maimonides Hospital is a university affiliated primary care hospital in Brooklyn with approximately 750 acute care beds including a full complement of intensive care units. The Microbiology Laboratory receives approximately 1,200 blood cultures per month. We reviewed the records of positive blood cultures processed over a six-month period (December 1989 to May 1990). Forty-eight of those blood cultures were positive for enterococci.

The organisms were regrown in broth from the nutrient media in which they are routinely stored in the laboratory. All were bile esculin positive, 6.5% saline positive, and catalase negative. The organisms were then tested for high-level gentamicin resistance and high-level streptomycin resistance using Mueller-Hinton agar screening plates impregnated with varying concentrations of gentamicin and streptomycin.

It was found that of the 48 isolates, 30 (63%) were resistant to 2,000 ug/ml streptomycin and 26 (54%) were resistant up 2,000 ug/ml of gentamicin.

The incidence of high-level gentamicin resistance among enterococci is reported in the literature as ranging from 9% to 15%.¹⁻³ One group has previously reported a 55% incidence of high-level gentamicin resistance in Ann Arbor, Michigan.⁴ However, and incidence as high as 54% has not been previously reported in the New York City area.

All enterococci have low-level intrinsic aminoglycoside resistance. This is due to low-level uptake of the antibiotic by the enterococci.⁵ When aminoglycosides are given together with cell wall synthesis inhibitors such as penicillin or vancomycin, the uptake of aminoglycosides is enhanced resulting in improved killing of the enterococci. This explains the well known synergistic effect of cell wall synthesis inhibitors and aminoglycosides. High-level resistance to aminoglycosides on the other hand is an acquired trait. It is the result of aminoglycoside-modifying enzymes in the case of gentamicin with the additional mechanism of ribosomal resistance for streptomycin.⁵ Aminoglycoside modifying enzymes may confer resistance to a number of aminoglycoside antibiotics, thus resulting in multiply resistant organisms.

All the isolates were from blood cultures drawn on patients located throughout the hospital for standard indications. The isolates were felt to have originated from the following sites based on retrospective chart review: intravenous catheters in 35% of cases, skin ulcers and decubiti in 24%, urinary tract in 12%, gastrointestinal tract in 6%, and to be "primary" in 23% of cases.

From our chart review, we determined that the clinical course of these patients was not significantly different than that of patients who were infected with non-high-level aminoglycoside resistant enterococci. This observation would thus suggest that the expression of high-level aminoglycoside resistance does not correlate with a change in clinical virulence. We believe that the data are of clinical relevance as we have demonstrated a surprisingly high incidence of high-level gentamicin resistance to a degree that has not been reported before in New York City. The main clinical problem caused by these organisms, requiring intensive bacteriocidal therapy, is enterococcal endocarditis. In such cases, since aminoglycoside administration is of no value

because it does not give the desired synergistic effect, the clinician has few choices. One option is continuous infusion of high-dose intravenous ampicillin.⁵ An alternative is the combination of daptomycin and fosfomycin;⁶ however, experience with these nonlicensed agents in this setting is limited.

As a result of our findings, we are planning to institute routine screening for high-level gentamicin resistance in enterococci isolated at our hospital. We will also handle patients infected with these strains in an appropriate manner to prevent the further spread of these highly resistant enterococci within the hospital.

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Charitable medical care

TO THE EDITOR: I would like to bring to your attention the exemplary actions of a spinal surgeon, Dr Michael G. Neuwirth of New York City.

The story of my struggle to obtain treatment for my 16-year-old son, Zachary, began in the small English town of Bacup Lancashire, where Zac and I live, along with his mother and sister. In 1988, we noticed that Zac had a problem with his back. As he grew, his spine had a definite humped appearance, which at first we thought was bad posture. Consequently, his mother and I continually advised him to "stand up straight," and not to slouch. As the months went by, I could see that this condition was in fact worsening and that he was fast becoming a "hunchback."

After two visits to the Orthopedic Department of a local infirmary, we were told that nothing could be done. In the consultant's own words—it was best left alone. We were advised to buy him some weights so that he could build up his back muscles. In January of 1990, Zac was discharged from the outpatient's clinic, having received dubious advice, and no offer of treatment for the consultant's diagnosis of Severe Kyphotic Congenital Deformity. The condition was by now causing some lower back pain, and much distress due to his worsening physical appearance. Zac was frequently found to be looking sideways in a full-length mirror with tears welling up in his eyes.

It was extremely upsetting for his mother and I to watch our only son growing up with such a terrible deformity. The weeks went by, and I suppose we were all trying to come to terms with Zac's condition. I had done as the consultant had advised, bought some weight-training equipment, and proceeded to help Zac to devise an exercise routine. In the meantime, I asked our general practitioner if there was another spinal consultant that we could be referred to. He said that we had reached the end of the road and that any further referrals would be a waste of time.

Then, in March of this year, due to the publicity given to the singer, Gloria Estefan, when she broke her back in a road accident in the USA, I was made aware of the skills of Dr Michael G. Neuwirth. I decided to write to this man and ask if he might be able to help my son Zac. He quickly replied and said the he was interested, and he asked for x-ray films to be sent from England.

After a seven-week delay caused by lack of cooperation by the local infirmary, I duly sent copies of x-ray films

to Dr Neuwirth in New York. Within a few days, we received a telephone call from Dr Neuwirth telling us that, yes, something could be done for my son, although it could mean two operations. We were overjoyed by this wonderful news.

Consequently, I returned to our general practitioner with this information and asked why this could not be done in England. He then agreed to refer Zac to a nearby spinal unit. I telephoned this spinal unit and was informed that Zac could be given an early private consultation, but that there was a four-year waiting list for spinal surgery on the National Health Service. I was advised to try a surgeon in Harley Street London and was given a Harley Street telephone number. An appointment was made with this surgeon in London, and after examining Zac, he told us that he could perform the necessary surgery to halt the progressive condition and that surgery was indeed essential because there was already some pressure on his spinal cord, causing spasticity in his legs. The cost of this surgery we were told, would be a total of 15,000 sterling (about \$30,000).

We returned home to the north of England from London, and pondered about how we could raise the money to finance the surgery. The day after, I thought I should telephone Dr Neuwirth's secretary to tell him that we now knew that surgery was possible in England, and the choice was either a four-year wait on the National Health Service or 15,000 in Harley Street, London. Dr Neuwirth responded with this message, "if you can get your son Zac to New York, I will perform the surgery free of charge." We were overwhelmed, speechless, and tears streamed down my cheeks.

On September 5, 1990, we did indeed get Zac to New York, where in due course Dr Neuwirth carried out two successful operations. The first five-hour one separated disc segments of his vertebrae that were fused together anteriorly. The second, another five-and-one-half hour operation was when two steel rods were put in place to complete the surgery and correct what had been a 90-degree curve in his spine.

You see, not only did Dr Neuwirth give his services free, he also persuaded four other doctors and several hospital departments to do the same. The whole three-week stay in the hospital, including two operations, plus the necessary intensive care and after care were free of charge. When, after the second operation, I was anxiously pacing the floors of the hospital, awaiting news of how the surgery had progressed, Dr Neuwirth came to me to reassure me that everything had gone well. I shook his hand vigorously, thanked him profusely, and he replied, "It was my pleasure."

This man, Dr Neuwirth, seeks no recognition for his dedication and compassion, indeed he shies away from publicity, but I feel that his actions should not go unnoticed.

My son and I have just returned to England after a total of eight weeks in New York, where we were treated with the utmost consideration and kindness by everyone concerned. Zac can now look forward to the rest of his life with a straight back.

Thanks to Dr Neuwirth, our story has a happy ending.

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Reducing needlestick injuries among health care workers

The HIV epidemic has stimulated interest in the risk of blood-borne disease transmission among health care workers. The Centers for Disease Control (CDC) has confirmed at least 37 cases where health care workers have become infected with the human immunodeficiency virus (HIV) after exposure to the blood of patients with HIV infection.¹ However, an even greater risk to health care workers exists in relation to hepatitis B, although it has yet to receive the same amount of attention. The CDC has estimated that as many as 12,000 workers become infected annually with the hepatitis B virus (HBV) from occupational exposure to blood. Between 2,500 and 3,000 of these individuals develop acute hepatitis and more than 200 die as a direct or indirect consequence of HBV infection.² An overwhelming majority of the occupationally acquired HIV and HBV infections occur as a direct result of needlestick injuries. Furthermore, needlestick injuries have been linked to the transmission of at least 20 other pathogens.

Interest has recently been focused on strategies that reduce the likelihood of needlestick injuries. There have been a number of recent safety designs in devices that involve the use of needles. Unfortunately, data are limited on which approach or approaches lead to improved worker safety, yet are practical and acceptable in delivering patient care. Through recently enacted legislation, the New York State Department of Health, in collaboration with selected hospitals across the state, has the opportunity to evaluate various devices intended to reduce needlestick injuries in the health care setting. The participating hospitals are located in such areas as New York City, Rochester, Syracuse, and Long Island. The primary goal of this study is to increase worker safety by promoting the development of a cost-effective technology that will reduce the likelihood of blood exposure from needlesticks. A second goal is to develop a reproducible methodology that can be applied to the evaluation of such devices in the future so that comparisons can be made as the technology changes. A recent study by Jagger et al³ examined the types of devices commonly involved in needlestick injuries. These include disposable syringes, prefilled cartridge syringes (tubex), steel needle intravenous (IV) sets (butterfly), IV catheter stylets, vacuum tube phlebotomy sets for blood drawing, and needles used to connect segments of IV tubing. In this study, the device with the highest rate of injury per unit was the IV tubing/needle assembly followed by the phlebotomy sets. Disposable syringes accounted for the greatest number of injuries, but their high volume of use gave them the lowest rate of injury.

Although there is no single solution that will reduce the

inherent risk from such devices, there are a number of modifications that have the potential to eliminate or lessen the hazard associated with a specific device. These include the elimination of needles from IV delivery systems, such as the ones described above; recessed needles for connecting parts of the IV delivery system; sleeves that slide forward over the needle after use; and needles that can be withdrawn into a protective sheath during removal.

Study Description

Phase I of this study involves a product evaluation of the device or devices selected for study by participating institutions. Training on the proper use of the devices will be provided to workers either by the facility or by the manufacturer's representatives. Information concerning the ease of use, how the device affects dexterity and suggestions for improvement will be obtained through a written survey of all product users and an in-depth interview with a subset of those users. At the end of the evaluation period, the facility will provide information on the acceptability of the device(s) and a determination will be made on whether to continue its use through Phase II.

Subsequently, Phase II of the study will assess the impact of these devices on reducing occupational needlestick injuries. Facilities participating in this study (to include most, if not all, of the Phase I participants) will be required to follow and report prospectively needlestick/puncture injuries in workers. One of the selection criteria for this study requires that facilities have historical data on employee needlestick incidents for the previous three years in order to evaluate the device(s).

Results of this study will be summarized in a future edition of *Epidemiology Notes*. Further information may be obtained by contacting: AIDS Institute, New York State Department of Health, Clinical Education Unit, Corning Tower, Room 729, Empire State Plaza, Albany, NY 12237.

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Physical activity and health

In 1988, 75% of New Yorkers reported being at risk for sedentary lifestyle. Substantial data exist suggesting that regular physical activity contributes to disease prevention, promotes physical and psychological well-being, and contributes to appropriate body weight and energy level. Studies have also reported beneficial effects of regular physical activity on the prevention and management of coronary heart disease, hypertension, noninsulin-dependent diabetes mellitus, and osteoporosis. Sedentary people are approximately twice as likely as physically active people to die from coronary heart disease.¹ The Behavioral Risk Factor Surveillance System (BRFSS) collects data used to estimate and compare the number of people in selected demographic groups who are at risk for poor

health outcomes associated with a sedentary lifestyle. Thirty-seven health departments participated in the BRFSS in 1988 and 1989. BRFSS uses standard questionnaire methods to conduct monthly random-digit-dialing telephone interviews of adults 18 years of age and older. Four levels of physical activity were assessed:

- no physical activity;
- irregular physical activity (less than three times per week or less than 20 minutes per session);
- regular physical activity (20 or more minutes, three or more times per week but who exercised at less than 60% of an individual's cardiorespiratory capacity);
- top fitness, which includes meeting the 1990 health objectives for the nation by exercising at 60% of individual cardiorespiratory capacity for 20 minutes or more, three or four times a week.

A measure of sedentary lifestyle was created by combining no physical activity and irregular physical activity.

New York is the state with the highest level of sedentary lifestyles among the 37 participating BRFSS survey states. In 1989, 73% of New Yorkers reported sedentary lifestyles, which was 24% above the 59% median reported for all participating states, and placed New York second among the participating states. However, when the irregular physical activity category is combined with regular and top fitness level categories, 66% of New Yorkers were exercising at least at some minimal level.

The study provided the estimated proportion of people at risk for sedentary lifestyle by selected sociodemographic characteristics. Whereas minor differences were reported by sex, race, income and region, the data were suggestive of age, education, and marital status effects. For instance, in 1989, more than 80% of those aged 45 and over were at risk of sedentary lifestyle as compared with 69% of people aged 25–44 and 60% of people aged 18–24. Of those separated, widowed, or divorced, 82% were at risk compared to 60% of those married and 75% of married people.

Among regular exercisers, walking was the most frequently reported exercise (42%), followed by aerobics (9%), running or jogging (9%), bicycling (7%), and weight lifting (5%). Other activities were reported by a total of 3% or less of people surveyed.

The effects on morbidity and mortality of a sedentary lifestyle contribute to the rising cost of health care, job absenteeism, and poor job performance. Given the high prevalence of sedentary lifestyle among New Yorkers, it has become increasingly more important that people, health agencies, hospitals, community health centers, voluntary organizations, and the business community become better educated about the benefits of regular physical activity and initiate regular exercise programs. Participation is encouraged through the creation of walking clubs and development of fitness trails, including measured distance routes. In addition, exercise programs at the work site can be promoted through installation of showers and the availability of flexible lunch hours. Educating community and business leaders to the positive results of exercise, such as enhanced job performance and

other benefits of a healthy population, may help encourage the development of exercise programs.

In 1988, the Mary Lasker Heart and Hypertension Institute of the New York State Department of Health initiated the New York State Healthy Heart Program. A major component of the Healthy Heart Program is the community intervention initiative based in eight communities—rural, suburban, and urban—with a combined population of 1.2 million. These Healthy Heart Programs are making entire communities healthier by giving New Yorkers skills, information, and choices required for heart-healthy behavior. The intervention programs have encouraged entire communities to become more physically active by organizing walking clubs, exercise classes, and other fitness activities. It is important that state and local health agencies encourage and work in collaboration with organizations such as the YMCA, health centers, businesses, and parks and recreation departments to initiate and provide opportunities for healthful exercise activities.

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The Long Island breast cancer study: Hair dye use and cigarette smoking

The Long Island Breast Cancer study, a cooperative effort begun in 1984 between the New York State Department of Health, the Nassau County Department of Health, the Suffolk County Department of Health Services, and the Department of Preventive Medicine of the State University of New York at Stony Brook, was initiated to learn more about the occurrence of breast cancer in Nassau and Suffolk counties. Nassau County, a highly urbanized and affluent area, has for many years had breast cancer incidence higher than the statewide average, whereas breast cancer incidence for adjoining Suffolk County has been slightly above the statewide average. Risk factors investigated in the study include demographic and reproductive factors, family and medical histories, residence and various lifestyle practices. The following review concentrates on results pertaining to the practices of hair dye use and cigarette smoking.

Methods

The study was designed as a matched case-control epidemiologic study. Potential cases were defined as all female breast cancer cases diagnosed between January 1, 1984, and December 31, 1986, at any hospital in New York State who were residents of Nassau or Suffolk County. Controls were selected from the drivers' license files of the New York State Department of Motor Vehicles and matched to individual cases by county and single year of birth. Data were collected from a total of 1,420 cases and 1,420 controls. Analysis was restricted to cases who reported having had a valid driver's license in New York State, and their matched controls, since cases without a driver's license had been observed to differ from drivers in key lifestyle practices. Results are presented for each county separately.

Hair Dye Use

In Nassau County, results showed no difference in breast cancer risk between ever-users and never-users of

hair dyes overall, or in any single age group (under 50, 50-70, or over 70). Risk also did not increase with the increasing number of hair dye applications in the entire study population, or any age group. Controlling for known breast cancer risk factors (eg, ever/never having a live birth, number of live births, age at first live birth, education, age at menarche, history of benign breast disease, family history of breast cancer, obesity, cigarette smoking, alcohol consumption) did not appreciably alter the results.

In Suffolk County, results showed an elevated risk of breast cancer in women who had ever used hair dyes. Stratification by age group showed this risk to be significant only among women under age 50 at diagnosis, whereas there was no difference in risk among women 50 years of age and older.

Risk was significantly elevated among women of all ages with low and moderate numbers of exposures to hair dyes, but not among those with the greatest number of exposures. In individual age groups, risk was elevated among women under 50 with low and moderate numbers of exposures and among women age 50-70 with moderate numbers of exposures. These results remained after controlling for known breast cancer risk factors. These findings are not consistent with the pattern to be expected if hair dye use were directly associated with breast cancer risk, and most likely arose by chance or by association with another uncontrolled for risk factor.

Cigarette Smoking

In Nassau County, an elevated risk of breast cancer was found among women who had smoked cigarettes (current and former smokers combined) and among former smokers alone, although not among current smokers. Risk was not significantly elevated in any single age group.

When stratified by lifetime cigarette consumption (pack/years), risk was significantly elevated only among moderate smokers, and neither light nor heavy smokers. This risk among moderate smokers appeared in the 50-70 and over-70 age groups, but not in the under-50 group. These results remained after controlling for known breast cancer risk factors. Findings are not consistent with the pattern one would expect if smoking were directly related to breast cancer risk, and could have arisen by chance.

In Suffolk County, there was no difference in breast cancer risk between ever and never smokers or among current, former, and never smokers, either in the study population as a whole or in any age group.

When lifetime smoking history was considered, an elevated risk was observed only among light smokers, and not among moderate or heavy smokers. Among the separate age groups, light smokers of ages 50-70 showed an elevated risk, whereas moderate smokers in the same age group showed a significantly reduced risk. When known breast cancer risk factors were controlled for, the risk estimates for the light smokers were reduced to a nonsignificant level, whereas risk estimates for moderate and heavy smokers were not significantly different. Once again, findings are not consistent with the pattern to be expected if cigarette smoking were directly related with breast cancer risk, and could have arisen due to chance or to the association of light smoking with well known breast cancer risk factors.

Copies of the full report presenting the analysis of lifestyle factors may be obtained by contacting: Bureau of Cancer Epidemiology, New York State Department of Health, Corning Tower, Room 565, Empire State Plaza Albany, New York 12237-0608

Is It Better to Know?: The HIV Antibody Test

This pamphlet, available in English and Spanish, discusses the specifics of the HIV antibody test so that individuals can make an informed decision on whether or not to be tested. Information found in the pamphlet includes the benefits of testing, the rights of individuals, where anonymous counseling and testing as well as additional HIV/AIDS services are available, discrimination concerns, and other pertinent issues. Copies are available free of charge by contacting: AIDS Institute, New York State Department of Health, Corning Tower, Room 757, Empire State Plaza Albany, NY 12237-0684. (518) 474-3045

School of Public Health Summer Course Announcement

The Department of Epidemiology in the University at Albany's School of Public Health, a joint venture of the University and the New York State Department of Health, is collaborating with the Department of Health's Injury Control Program to offer the following summer course: Epidemiology 513, Epidemiologic Approaches to Injury Control, June 24-28, 1991.

This summer session is a one-week intensive training program designed for public health and health care professionals, particularly those in New York State, who are involved in injury control programs at the community level and have less than two years of recent experience in this field. The course, which offers two graduate credits, will train professionals and graduate students in the application of epidemiologic methods and principles in studying the etiology of injuries and developing strategies for their prevention and control. The course will draw on numerous case study examples to demonstrate proven interventions suitable for community application.

The summer session will be taught in Albany by faculty from the School of Public Health, the Injury Control Program, and invited lecturers from successful community programs in New York State. Topics include Nature and Etiology of Injuries; Injury Surveillance—Working with Data/Setting Priorities; Prevention Strategies; Program and Project Design, Implementation and Evaluation; Motor Vehicle Injuries; Recreational Injuries; Home Injuries; Occupational Injuries; Intentional Injuries—Homicide/Assault and Suicide; Public Health Policy and Practice; and Engineering and Biomechanics. For further information, contact: Helga Straif-Taylor School of Public Health, Two University Place, Albany, New York 12203-3399. (518) 458-6772

ALTON OCHSNER. SURGEON OF THE SOUTH

By John Wilds and Ira Harkey. 268 pp, illustrated. Baton Rouge, Louisiana, Louisiana State University Press, 1990. \$24.95 (hardcover)

This remarkable biography of one of the now legendary American surgeons was started by Ira Harkey and completed by Dr John Wilds. The authors knew Dr Ochsner for many years and supplemented their intimate knowledge of his life with interviews and correspondence with more than 500 people who knew him well. All the members of the Ochsner family contributed intimate details of their relationship with this "Surgeon of the South." Dr Alton Ochsner himself is said to have been the principal contributor to interviews, mainly with Ira Harkey. The result is an intimate picture of a world-famous surgeon, which lacks only one ingredient, unfortunately one lacking in many biographies, namely, a true understanding of the motivating factors that drove this gifted individual to such great heights of accomplishment. Its principal purposes would be to inspire the young, to encourage the middle aged, and to enhance the reminiscences of the more elderly. It is, throughout, an entertaining book. In many ways it is extremely personal, although sometimes seemingly intrusive on the lives of the members of the Ochsner family. It outlines Professor Ochsner's genealogy and follows the 85 years of his life, emphasizing his strong and assertive personality, his sense of humor, his unwillingness to compromise his obviously tenaciously held ideas and lofty ideals. It points out his rather firmly held and generally accurate insights, exemplified by his conviction regarding the harmful effects of smoking when the notion was new and considered irrational.

Having been on the visiting faculty at the Ochsner Clinic many years ago during Dr Alton Ochsner's lifetime, I can remember on one of my visits, having been graciously invited to lunch with him at his favorite club. Naively unaware of his firm conviction about the evils of smoking, I lit an after dinner cigarette. This invited a kindly paternal but firm lecture on the evils of smoking.

For years afterward when we met, he never forgot to inquire whether I had become a confirmed nonsmoker.

Without a doubt, Dr Alton Ochsner would have to be classified as one of the great men of our times and, as such, one cannot expect his life to have been directed at achieving popularity. Nevertheless, he was an immensely popular figure. It is clear from this volume that he was a man firmly committed to the development of the craft and science of surgery, sometimes to the exclusion of other activities, the mark of a great achiever.

In general, it is a successful biography. I have checked with a member of the Ochsner family regarding their concept of the book. It is said to be a very popular volume in New Orleans. There are only two areas of criticism from their point of view, areas in which the authors have presented unbalanced or unfair versions. One has to do with the allegedly strained relationship between Dr Ochsner's two sons, Akkey and John, and the other with his role as a prime cause of the divorce of his daughter, Sis, from her husband. In both instances, the circumstances were more complex than presented in the book, and add to rather than detract from the picture of a closely knit family unit.

Additionally, the authors intimate, probably unfairly, that nepotism played a great role in the successes of various members of the Ochsner clan. It is more likely, however, that the natural and normal inclination of devoted family members to be helpful to each other resulted in such spectacular results, and that because of their native talents this aura appears.

It is recommended reading for both medical and nonmedical readers, as being insightful into the life of a highly successful surgeon, as well as into a number of historical medical events. It is also entertaining and readable.

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LASERS IN SURGERY

Edited by Stephen N. Joffe, MD. 319 pp, illustrated. Baltimore, MD, Wil-

liams & Wilkins, 1989. \$65.00 (hardcover)

Newspaper and magazine articles appear daily describing the advantages of "state of the art" laser surgery. They claim that laser surgery is painless, associated with less blood loss and therefore allows for a faster recovery and return to normal activities. Our patients read these articles and ask for and sometimes demand laser treatment for various problems including gallbladder disease, hemorrhoids, and breast disorders. Dr Joffe has put together an excellent overview of medical lasers. His primary objective is to provide general surgeons "with current, substantive, and practical guidance in the comprehension and use of lasers in general surgery." This is quite an undertaking, but he has done an able job.

The first ruby laser was invented less than 30 years ago and its medical applications are rapidly evolving. Dr Joffe and the 50 other authors of the 30 chapters in this volume have a large clinical experience with the various types of lasers. Most of this international group of authors have faculty appointments at medical schools, although most of the chapters describe personal series of uncontrolled and nonrandomized patients.

The book attempts to be comprehensive, beginning with a description of the different types of surgical lasers, including a listing of various laser models with the manufacturers' telephone numbers and addresses. It then goes on to cover laser safety, describing some of the physics and hazards of laser use. The majority of the book discusses laser applications for different disease entities, including breast surgery, gallbladder disease, applications for advanced intra-abdominal tumors, liver resection and pancreatic surgery. There are four chapters devoted to anorectal surgery emphasizing laser hemorrhoidectomy. I find it interesting that laser hemorrhoidectomy is emphasized more than palliation of obstructing esophageal and rectal carcinomas. There is a short chapter on laparoscopic surgery and then several chapters concerning laser usage for vascular surgery. There is a very good chapter on dermatological disorders. There are two chapters on

photodynamic therapy and laserthermia which are very interesting and have potential applications in the future for tumor ablation. The final few chapters concern wound healing, nursing care, and perioperative anesthesia and analgesia.

This book is an excellent overview for the surgeon who wants to begin using lasers. It explains the different features of the Nd:YAG, CO₂, argon, KTP, and dye lasers, and is a good reference if one is in the market for a new laser. The book also explains some of the advantages of contact versus noncontact laser fibers. The references accompanying the chapters clarify the operative techniques and substantiate some of the claims made concerning the benefits of laser treatment.

There are more than the usual number of typographical errors, and this is occasionally annoying. The listing of contributors at the beginning of the book omits several of the authors of chapters. In spite of these problems, this book is a very good overview of a broad and rapidly increasing field.

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NUCLEAR MEDICINE ANNUAL 1990

Edited by Leonard M. Freeman, MD. 256 pp, illustrated. New York, Raven Press, 1990. \$98.00 (hardcover)

This work is the 11th in a series annually produced since 1980. Like its predecessors, it consists of a series of review articles on selected topics in nuclear medicine by a group of authors who are well known and well qualified in their given areas. Each of the nine chapters presents a review of pertinent literature, experiences of the author(s), and opinions based on both. All are extensively referenced.

In general, the subject matter is quite specialized. The nine chapters cover aspects of bone scanning in osteoporosis, nuclear imaging in acquired immunodeficiency syndrome (AIDS), brain imaging with HMPAO, assessment of coronary angioplasty using myocardial imaging, tumor immunoscintigraphy, intraoperative tumor detection with probes, detection of osteomyelitis by scanning, measurement of glomerular filtration rates with radiopharmaceuticals and radionuclide cystography. Although the approach is highly selective, many other sources deal with the more

mundane fare omitted from the volume. Indeed, the uniqueness and utility of this work is exactly that, surely by design of the editor, who has had two decades of experience as editor of *Seminars in Nuclear Medicine*.

Each chapter is lucid and well written. The authors manage to expound thoroughly on their subject matter and with clarity of expression, without engaging in unnecessary digressions or useless detail. Some statements are unconventional, reflecting the experiences of each author, but none are unreasonable. Indeed, such unorthodoxy, when it occurs, is both refreshing and provocative. The quality of the illustrations is good in all cases, excellent in many, and the quality of printing is likewise excellent. Moreover, this reviewer could not find a single typographical error. Obviously, a good deal of care went into the publication.

This work is intended neither for a general medical audience nor for one seeking to learn the basics of nuclear medicine. It presumes considerable knowledge of a dynamic and rapidly evolving specialty and is directed toward practicing nuclear physicians. Other specialists may find considerable value in individual chapters—eg, urologists and nephrologists in the one on glomerular filtration rates by Summer-ville, Potter, and Treves and in the one on cystography by Sty and Wells. As a nuclear physician, I found the book to be both very useful and up to date.

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DIABETES MELLITUS IN THE ELDERLY: A PRACTICAL GUIDE

Edited by Steven R. Gambert, MD. 288 pp, illustrated. New York, Raven Press, 1990. \$69.00 (hardcover)

Despite the overwhelming tide of a high-tech medical revolution, two trends have become abundantly clear: America is aging, and the focus of medical care is now ambulatory. Primary care physicians must orient, or in some cases reorient, their thinking to the 12% of our population who are over 65 years of age and who consume a 30% of medical services.

Diabetes Mellitus in the Elderly: A Practical Guide is a very practical and successful attempt to present, in a concise and readily useful format, a state-of-the-art guide for physicians, physi-

cians assistant, nurses, and students of medicine. It is an easy read.

The chapters on the diabetic foot, end-stage renal disease and peripheral and autonomic neuropathy are superb and the treatment of hyperosmolar nonketotic coma is so complete as to also include the gray area of ketotic hyperosmolar states as well.

I am perhaps addressing my own prejudices as a geriatrician when I say that a more elaborate treatment of autonomic dysfunction would have been welcomed. This is particularly relevant with regard to orthostatic hypotension, which with its deplorable toll of head traumas and hip fractures, is so often overlooked in the routine geriatric physical. It is a diagnosis often made only after a preventable disaster has occurred. This volume, with its extensive use of well-developed tables and flow-sheets, would gain by the inclusion of a brief table of screening tests for autonomic dysfunction with, perhaps, a few clinical pearls on sweating abnormalities.

The editors are to be commended. The integration of the feelings and preferences of so many high-powered authorities into a cohesive whole with a minimum of duplication is a significant academic accomplishment. This small book is a large addition to the growing geriatric literature. It has the capability of making us all just a little bit better.

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ANTI-RHEUMATIC DRUGS

Edited by M. Orme. 241 pp, illustrated. Elmsford, NY, Pergamon Press, Inc, 1990. \$67.50 (hardcover)

The purpose of this book is to extend the knowledge of basic scientist and clinician about concepts of therapy for rheumatic diseases. This is a multi-authored volume written by authoritative contributors from the United Kingdom and Australia. The contents of this 233 page book vary from extensive descriptions of models of arthritis to the significance of cytokines in rheumatic disease. Yet, it also includes complete reviews of anti-inflammatory and anti-rheumatic drugs and an assessment of their efficacy. Each chapter is extensively referenced and contains an admirable and complete review of the topic and the state of literature related to it. Whereas I feel that this book would be

quite helpful to rheumatologists, family practitioners, and internists may find the data to be a bit too complex for general use.

Overall, I found the information compiled in each chapter to be quite extraordinary in its depth and its correctness. I was somewhat surprised, however, at some of the statements made about anti-rheumatic drugs in Chapter 5 by Dr Littler. In the section on methotrexate, he makes little mention of the major impact of this drug on the care and treatment of patients with rheumatoid arthritis throughout the world. This may reflect the role of methotrexate in the armamentarium against rheumatoid arthritis in the United Kingdom, but certainly does not deliver to the reader the data about this medication and its impact on the rheumatology community in the United States. Although the publishing date is 1990, this chapter may very well have been written prior to the increased use of this medication in the treatment of active rheumatoid arthritis.

As a rheumatologist, I have found this book to be quite helpful, and I especially enjoyed the chapters on models of arthritis and cytokines and their significance in rheumatic disease. Aside from the point noted above, I do feel that this is an excellent addition to the literature and would be of particular interest to practicing rheumatologists or basic scientists wanting to learn more about the clinical aspect of rheumatologic disorders and their treatments. General practitioners, family practice physicians, and internists may also find parts of these chapters to be quite helpful in expanding their knowledge about the complex issue of the treatment of rheumatologic disorders.

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HYPOCHONDRIA—WOEFUL IMAGINING

By Susan Baur. 260 pp, Berkeley, CA, University of California Press, 1988. \$9.95 (softcover) \$25.00 (hardcover)

It may seem bizarre for even a book reviewer to pick up a volume entitled *Hypochondria* as Sunday reading, but this reader is quite glad she did. The subtitle, *Woeful Imaginings*, gives some indication of the novel approach to one of medicine's most difficult aberrations, the patient who is wedded to his

misery. The author, Susan Baur, according to the biographical notes on this easily portable softcover, is a doctoral candidate in counseling psychology at Boston college, a professional track that would seem to bear little connection to the many talents used in producing an eminently charming, informative, and thoroughly readable piece of work.

Baur explores the long, in fact, antique art of building a life around one's imagined pathology, giving it the respect it deserves as a ubiquitous culture and intelligence-transcending phenomenon, deeply rooted in all civilizations and all epochs. Identifying some of the world's most important hypochondriacs, quoting from their diaries and letters, giving details of their medicinal peregrinations, she subtly informs us that the thickness of a man's chart is in no way an indication of his usefulness to society or of his worth to his family. Where would this world be without Darwin, Tolstoy, Boswell, Alice James . . . the list goes on and on.

She cleverly explores the etiology, pathophysiology, clinical course, and outcome of the disease itself, discussing its utility to the sufferer, and the Machiavellian productivity it can achieve. She makes the crock become almost a loveable pet, with her wisdom and understanding of the suffering for which nagging doubt and repetitive hospital and doctor visits provides real, if temporary, surcease.

Unlike the subjects of her unlikely inquiry, the author provides an organized table of contents to her volume. They are Being a Hypochondriac; A Disease So Grievous, So Common; The Social Significance of Being Ill; Pathways Toward Childhood Hypochondria; Hypochondria in the Family; Hypochondriacs and Their Doctors; Hypochondria Among the Elderly; Hypochondria and Other Cultural Values; Hypochondria in Other Cultures; Occupational Hypochondria; and Getting Better. She also thoughtfully provides a superb appendix, notes and bibliography for those readers who have been converted to a genuine love for sufferers of this psychologically leprous disease and are desirous of learning more. She is so convincing. One can even envision the formation of a new specialty board entitled The American Board of Hypochondriatrists.

The reader would be happy to apply for membership. Highly recommended.

NAOMI BLUESTONE, MD
Consulting Editor

JOSLIN DIABETES MANUAL. TWELFTH EDITION

By Leo P. Krall, MD, and Richard S. Beaser, MD. 406 pp, illustrated. Philadelphia, PA, Lea & Febiger, 1989. \$10.95 (paperback)

The twelfth edition of this manual is an updated revision of a resource for patients which was first published in 1918 to "help people survive." With the discovery of insulin and major clinical advances in the last seventy years, the face of diabetes and certainly its treatment have changed. The purpose of this manual is education for the patient, education as a form of treatment. The authors are the physicians and staff of the Joslin Diabetes Center (over 100 individuals acknowledged), which is well known for a tradition of clinical and research excellence. Recognized most prominently are Dr Leo Krall, Chairman of the Board for the Diabetes Research and Education Foundation; and Dr Richard Beaser, Chairman of the Patient Education Committee of the Joslin Diabetes Center.

Unlike many books reviewed in the *Journal*, this volume is meant for the patient. It is written in a style and language easily understood by a high school graduate. The manual emphasizes diet, exercise, and living with diabetes, understanding the chronicity of the disease and the skills and attitudes necessary for the patient to maximize their health status. All people with diabetes can benefit from reading this book, thus it is a valuable addition to the patient education literature.

The 365 pages of this manuscript are organized into 19 informative chapters that deal with up-to-date, practical "everyday" issues for patients. Chapter 1 defines diabetes, its types, and its possible etiologies. The sections that follow discuss treatment, and the roles of education, nutrition, and exercise. The importance and "how-to" aspects of self-monitoring of blood glucose is stressed. The most appropriate pharmacologic management of diabetes according to the type of disease is dealt with simply yet accurately in chapters 10 and 11. A discussion of diabetes in the special situations of youth, pregnancy, and the aged follows, and as before, always with a positive attitude that promotes independence and control over one's disease.

With this background established, the last portion of the manual discusses the acute and chronic complications of

diabetes, not as a threat to the neglectful individual, but rather from the perspective of the rewards of the development of a healthy lifestyle.

The material presented in this book is accurate, comprehensive, yet easy to understand. It is a bit lengthy for most patients to read from beginning to end, although without question it represents a useful reference source for diabetics. I am uncomfortable with the "Insulin

Adjustment Guidelines" provided for patients in chapters 9 and 13, and although they alter their insulin regimen without consulting with their personal physician first. I also noted that not all abbreviations on the retina photographs (p. 276, Figure 15.5) were defined in the legend.

The twelfth edition of the *Joslin Diabetes Manual* is a well-organized, easy to read, comprehensive, and accurate

resource for diabetics. This text provides a wholesome, educational, optimistic approach to diabetes, which is a welcome addition to the body of patient educational literature.

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FROM THE LIBRARY

CRYPTOCOCCOSIS

Cryptococcosis (torulosis) caused by *Cryptococcus neoformans* is usually a primary pulmonary infection but may be cutaneous, subcutaneous, or mucosal. The primary pulmonary lesion may be inconsequential or never detected, and the patient appears with a brain or meningeal lesion. Some of the recognized pulmonary lesions have been cured by surgical resection and others with vaccine, iodides, and sulfadiazine.

An occasional patient with cryptococcus meningitis achieves a biologic balance with the fungus and remains alive for years but subject to periodic recurrence of symptoms and reappearance of the organism in the spinal fluid. An occasional patient has recovered after treatment with sulfadiazine or actidione.

Streptothricin is effective in the test tube and has cured some experimentally infected mice but is probably too toxic to be used in man. Propamidine inhibits the growth of *C. neoformans* in media in the presence of serum. We have treated two moribund patients who died on the third day of therapy. The patients were so ill that it was not possible to evaluate either the harmlessness of the drug or its therapeutic effectiveness.

DAVID T. SMITH
(*NY State J Med* 54:2307)

AIDS

Private Acts, Social Consequences: AIDS and the Politics of Public Health. By Ronald Bayer. 302 pp. New Brunswick, NJ, Rutgers University Press, 1989. \$14.95 (softcover)

CARDIOLOGY

Arrhythmias: Case Studies in Management (software program). By Edward P. Hoffer, MD, and G. Octo Barnett, MD. Baltimore, Md, Williams & Wilkins Electronic Media, 1985. \$98.50

CARDIOTHORACIC SURGERY

Mediastinal Surgery. Edited by Thomas W. Shields, MD, DSC (Hon). 400 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$85.00 (hardcover)

GERIATRICS

The Merck Manual of Geriatrics. Edited by William B. Abrams, MD, Robert Berkow, MD, and Andrew J. Fletcher, MBB CHIR. 1,267 pp. Rahway, NJ, Merck Sharp & Dohme Research Laboratories, 1990. \$20.00 (hardcover).

INTERNAL MEDICINE

Pulmonary Manifestations of Systemic Disease: A Clinical Approach. Edited by Kevin R. Cooper, MD. 240 pp, illustrated. Mount Kisco, NY, Futura Publishing Company, 1990. \$48.00 (hardcover)

Diving Medicine. Second Edition. By Alfred A. Bove, MD, and Jefferson C. Davis, MD. 352 pp, illustrated. Philadelphia, Pa, WB Saunders, 1990. \$50.00 (hardcover)

Chest Pain: An Exercise in Clinical Problem-Solving (software program). By S. Pierre Pinetel, MD, in cooperation with Edward P. Hoffer, MD, and G. Octo Barnett, MD. Baltimore, Md, Williams & Wilkins Electronic Media, 1987. \$98.50

MEDICAL ETHICS

Ethics Consultation in Health Care. Edited by John C. Fletcher, PhD, Norman Quist, and Albert R. Jonsen, PhD. 209 pp. Ann Arbor, Mich, Health Administration Press, 1989. \$24.00 (hardcover)

MEDICAL HISTORY

The Body and Surgery in the Middle Ages. By Marie-Christine Pouchelle. 300 pp, illustrated. New Brunswick, NJ, Rutgers University Press, 1990. \$40.00 (hardcover)

A History of Vascular Surgery. By Steven G. Friedman, MD. 212 pp, illustrated. Mount Kisco, NY, Futura Publishing Company, 1989. \$27.50 (hardcover)

MISCELLANEOUS

Calories and Carbohydrates. Ninth Revised Edition. By Barbara Kraus. 425 pp. New York, Penguin Group, 1991. \$9.95 (softcover)

Having A Cesarean Baby. The Complete Guide for a Happy and Safe Cesarean Childbirth Experience. Second and Revised Edition. By Richard Hausknecht, MD, and Joan Rattner Heilman. 213 pp, illustrated. New York, Penguin Group, 1991. \$9.95 (softcover)

How to Raise An Adopted Child: A Guide to Help Your Child Flourish From Infancy Through Adolescence. By Judith Schaffer and Christina Lindstrom. 310 pp. New York, Penguin Group, 1991. \$8.95 (softcover)

The Cholesterol Conspiracy. By Russell L. Smith, PhD, and Edward R. Pinckney, MD. 400 pp, illustrated. St Louis, Mo, Warren H. Green, Inc, 1991. \$37.50 (softcover)

What's New in Medicine: More than 250 of the Biggest Health Issues of the Decade. By L. A. Chotkowski, MD. 274 pp. Santa Fe, NM, Health Press, 1991. \$14.95 (softcover)

The Art and Science of Bedside Diagnosis. By Joseph D. Sapira, MD. 601 pp, illustrated. Baltimore, Md, Urban & Schwarzenberg, 1990. \$49.50 (hardcover)

Black Women in White: Racial Conflict and Cooperation in the Nursing Profession, 1890-1950. By Darlene Clark Hine. 288 pp, illustrated. Bloomington, Ind, Indiana University Press, 1989. \$35.00 (softcover)

Communication and Education Skills: The Dietitian's Guide. Second Edition. By Betsy B. Holli, EdD, RD, and Richard J. Calabrese, PhD. 269 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$22.50 (softcover)

NEUROLOGY

The Human Nervous System: Introduction and Review. Fourth Edition. By Charles R. Noback, PhD, Norman L. Strominger, PhD, and Robert J. Demarest. 448 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$34.50 (softcover)

NEUROSURGERY

Meningiomas. Edited by Ossama Al-Mefty, MD. 652 pp, illustrated. New York, Raven Press, 1991. \$135.00 (hardcover)

OPHTHALMOLOGY

Advances in Ophthalmic Plastic and Reconstructive Surgery: The Anophthalmic Socket. Volume 8. Edited by Stephen L. Bosniak, MD, and Byron C. Smith, MD. 288 pp, illustrated. Elmsford, NY, Pergamon Press, 1990. \$75.00 (hardcover)

Phacoemulsification Surgery. Edited by Ter-

ence M. Devine, MD, and William Banko, MD. 130 pp, illustrated. Oxford, England, Pergamon Press, Inc, 1991. \$125.00 (hardcover)

ORTHOPEDIC SURGERY

The Lumbar Spine: The International Society for the Study of the Lumbar Spine. By James N. Weinstein and Sam W. Wiesel. 1,072 pp, illustrated. Philadelphia, Pa, WB Saunders, 1990. \$130.00 (hardcover)

PATHOLOGY

Robbins Pathologic Basis of Disease. Fourth Edition. By Ramzi S. Cotran, MD, Vinay Kumar, MD, and Stanley L. Robbins, MD. 1,536 pp, illustrated. Philadelphia, Pa, WB Saunders, 1989. \$64.50 (hardcover)

PEDIATRICS

Problem-Oriented Pediatric Diagnosis. By Roger M. Barkin, MD, MPH. 306 pp, illustrated. Boston, Mass, Little, Brown and Co, 1990. \$22.50 (softcover)

PHYSIOLOGY

McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. Third Edition. By Wilmer W. Nichols, PhD, and Michael F. O'Rourke, MD. 456 pp, illustrated. Malvern, Pa, Lea & Febiger, 1990. \$98.50 (hardcover)

PSYCHIATRY

Swimming Upstream: Teaching and Learning Psychotherapy in a Biological Era. By Jerry M. Lewis, MD. 208 pp, illustrated. New York, Brunner/Mazel Publishers, 1991. \$25.00 (hardcover)

Prevention in Community Mental Health Centers. Edited by Robert E. Hess, PhD, and John Morgan, PhD. 138 pp. Binghamton, NY, The Haworth Press, Inc, 1990. \$24.95 (hardcover)

The Mental Health Professional and the Legal System. By the Group for the Advancement of Psychiatry Committee on Psychiatry and the Law. 208 pp. New York, Brunner/Mazel Publishers, 1991. \$25.00 (hardcover)

RADIOLOGY

Magnetic Resonance Imaging of the Brain and Spine. Edited by Scott W. Atlas, MD. 1,151 pp, illustrated. New York, Raven Press, 1991. \$165.00 (hardcover)

SURGERY

Infectious Risks in Surgery. By Richard J. Howard, MD. 294 pp, illustrated. East Norwalk, Conn, Appleton & Lange, 1991. \$49.95 (hardcover)

A colobronchial fistula associated with Crohn's colitis

Fistulas develop in about one third of patients with Crohn's disease. A colobronchial fistula is a rare complication of the disease (*Am Rev Respir Dis* 1990; 142:1225-1227).

Initially, bronchopneumonia developed in the left lower lobe of the lung in this patient, who had been diagnosed as having inflammatory bowel disease five years earlier. A chest radiograph demonstrated a large pleural effusion and pneumonic infiltrates in the left lower lobe. Antibiotic therapy was unsuccessful. Microscopic analysis of the sputum identified fecal-like material. Computed tomography with barium contrast revealed "a fistula from the left colonic flexure, along the lateral border of the spleen, and up through the diaphragm into the left bronchial system." There was also a fistula between the left colonic flexure and the stomach.

Lobectomy of the left lower lobe and partial colectomy were followed by postoperative sepsis, renal failure, and myocarditis. Three months after surgery, the patient was discharged from the hospital.

Normal plasma cholesterol levels in a man who eats about 25 eggs a day

An 88-year-old man has eaten 20-30 soft-boiled eggs each day for more than 15 years, in what a psychiatrist describes as a compulsive behavior (*N Engl J Med* 1991; 324:896-899). An assessment of the man's plasma lipid levels yielded the following results: total cholesterol, 200 mg/dL; low-density lipoprotein (LDL), 142 mg/dL; and high-density lipoprotein (HDL), 45 mg/dL.

By studying the man's cholesterol consumption, biosynthesis, metabolism, and excretion, the authors were able to hypothesize how his body compensates for the extremely high cholesterol diet. The main mechanisms found were dramatically reduced cholesterol absorption, increased bile acid synthesis, and reduced cholesterol synthesis.

The man absorbed only 18% of the dietary cholesterol, compared to 46.4% mean absorption by a study population on a high cholesterol diet. The cholesterol not ab-

sorbed would be excreted in the feces. The body would convert some of the cholesterol synthesized or absorbed into bile acids; this mechanism normally processes about 70% of the cholesterol excreted each day. The rate of bile acid synthesis in the man described here was nearly twice the rate of synthesis in the study population, enabling him to dispose of increased quantities of cholesterol.

In spite of the huge amount of cholesterol ingested, this man had normal plasma cholesterol levels and, remarkably, had no clinical evidence of atherosclerosis.

Monoclonal antibody significantly reduces mortality due to septic shock

Even with conventional treatment—aggressive antibiotic therapy and intensive supportive care—the mortality rate for patients with sepsis and gram-negative bacteremia ranges from 20% to 60%. The incidence of septicemia is continually rising, with about 400,000 cases documented per year in the United States.

Septicemia occurs when pathogens enter the blood stream, as can occur during surgery or as the result of a wound. Gram-negative bacteremia occurs in approximately 30% of cases of septicemia. HA-1A, or Centoxin (Centocor; Malvern, Pa), is a monoclonal antibody that binds endotoxin, prompting its removal from the bloodstream.

In a prospective, randomized, double-blind, controlled clinical trial, Ziegler et al demonstrated 39% reduced mortality with HA-1A in 200 patients with sepsis and gram-negative bacteremia (*N Engl J Med* 1991; 324:429-436). Twenty-eight days after infusion with HA-1A, 49% of placebo recipients had died, compared to 30% of HA-1A recipients. HA-1A was associated with a 42% reduction in mortality among patients with gram-negative bacteremia who were also in shock before treatment. There were no serious adverse reactions in all 291 patients who received HA-1A. "These findings illustrate the potential of human monoclonal immunotherapy in clinical medicine," the authors conclude.

OBITUARY LISTINGS

Hyman Ashman, MD, New York. Died March 29, 1991; age 82. Dr Ashman was a 1934 graduate of Columbia University College of Physicians and Surgeons. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

James Lewis Blanton, MD, Cincinnati, Ohio. Died November 23, 1990; age 92. Dr Blanton was a 1924 graduate of the Virginia Commonwealth University, Medical College of Virginia School of Medicine, Richmond, Virginia. He was a member of the Ontario County Medical Society and the Medical Society of the State of New York.

Morris Bonfield, MD, Fort Lauderdale, Florida. Died March 2, 1991; age 91. Dr Bonfield was a 1925 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Thelma Brock, MD, Williamsville. Died March 22, 1991; age 86. Dr Brock was a 1928 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. She was a Fellow of the American College of Allergists. Her memberships included the New York State Society of Internal Medicine, the American Academy of Allergy, the American Society of Internal Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Annie Louise Brush, MD, Greenwich, Connecticut. Died October 1, 1990; age 89. Dr Brush was a 1929 graduate of Columbia University College of Physicians and Surgeons. She was a Diplomate of the American Board of Psychiatry and Neurology. Her memberships included the American Psychiatric Association, the American Geriatrics Society, the New York County Medical Society, and the Medical Society of the State of New York.

Vincent J. Geraci, MD, Glen Cove. Died April 23, 1991; age 77. Dr Geraci was a 1942 graduate of Middlesex University School of Medicine, Waltham, Massa-

chusetts. He was a Fellow of the American Academy of Family Physicians. He was a member of the American Geriatrics Society, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Janina Gidynski, MD, New York. Died January 15, 1991; age 92. Dr Gidynski was a 1926 graduate of the Akademia Medyczna Wydział Lekarski, Poznan, Poland. She was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

David Hauptman, MD, Hauppauge. Died April 8, 1991; age 86. Dr Hauptman was a 1930 graduate of Tufts University School of Medicine, Boston. He was a Diplomate of the American Board of Pediatrics and a Fellow of the American Academy of Pediatrics. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Frederic Norman Kansler, MD, Huntington. Died April 6, 1991; age 54. Dr Kansler was a 1964 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Diplomate of the American Board of Radiology. He was a member of the New York Roentgen Society, the Nassau County Medical Society, and the Medical Society of the State of New York.

Emanuel P. La Motta, MD, Somerset, New Jersey. Died April 12, 1991; age 84. Dr La Motta was a 1931 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. His memberships included the New York Academy of Medicine, the New York Cardiological Society, the Clinical Society, New York Diabetes Association, the American Rheumatism Association, the American Geriatrics Society, the New York County Medical Society, and the Medical Society of the State of New York.

John Walter Lawson, MD, Yonkers. Died March 22, 1991; age 91. Dr Lawson was a 1925 graduate of McGill University, Faculty of Medicine, Montreal, Quebec, Canada. He was a mem-

ber of the New York Academy of Medicine, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Virginia C. Lent, MD, Pasadena, California. Died July 9, 1990; age 79. Dr Lent was a 1938 graduate of New York University School of Medicine. She was a Diplomate of the American Board of Pediatrics, a Diplomate of the American Board of Allergy & Immunology, and a Fellow of the American Academy of Pediatrics. She was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Ned Arthur Lewis, MD, Forest Hills. Died March 1, 1991; age 88. He was a 1929 graduate of George Washington University School of Medicine and Health Science, Washington, DC. He was a member of the American Geriatrics Society, the American Academy of Family Physicians, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Evan W. McLave, MD, Southold. Died October 3, 1990; age 95. Dr McLave was a 1919 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Internal Medicine. He was a member of the New York Academy of Medicine, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Arthur Murray Meisel, MD, Brooklyn. Died March 21, 1991 age 68. Dr Meisel was a 1945 graduate of Tulane University School of Medicine, New Orleans, Louisiana. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychiatric Association, the American Geriatrics Society, the Association for Research in Nervous and Mental Disease, the American Psychoanalytic Association, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Kate Freeman Miller, MD, Coconut Grove, Florida. Died November 3, 1990; age 90. Dr Miller was a 1926

graduate of New York University School of Medicine. She was a Diplomate of the American Board of Dermatology, Inc. She was a member of the New York Academy of Medicine, the American Academy of Dermatology, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Alexander Mintzer, MD, Hollywood. Died March 1, 1991; age 84. Dr Mintzer was a 1930 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Samuel Pearl, MD, New York. Died July 23, 1991; age 87. Dr Pearl was a 1928 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Ellis D. Rand, MD, Huntington. Died April 12, 1991; age 80. Dr Rand was a 1933 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Orthopedic Surgery, a Fellow of the American College of Surgeons and a Qualified Fellow of the International College of Surgeons. He was a member of the American Academy of Orthopaedic Surgeons, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Zoltan Rubin, MD, Astoria. Died March 25, 1991; age 82. Dr Rubin was a 1934 graduate of Friedrich-Wilhelms Universitaet Medizinische Fakultae, Berlin, Germany. His memberships included the New York State Dermatological Society, the American Academy of Dermatology, the Academy of Psychosomatic Medicine, the American Society of Clinical Hypnosis, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Robert Joseph Schaffer, MD, Auburn. Died February 27, 1991; age 75. Dr Schaffer was a 1942 graduate of Cornell University Medical College. He was a member of the Medical Society of the County of Cayuga and the Medical Society of the State of New York.

Julius Schoenfeld, MD, Brooklyn. Died March 19, 1991; age 85. Dr Schoenfeld was a 1929 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the American Society of Abdominal Surgeons, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Gertrude M. Shults, MD, Lakemont. Died April 14, 1991; age 91. Dr Shults was a 1928 graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland. She was a member of the Medical Society of the County of Yates and the Medical Society of the State of New York.

Alexander Singer, MD, Brooklyn. Died March 2, 1991; age 83. Dr Singer was a 1930 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Alexander Slanger, MD, Hollywood, Florida. Died March 1, 1991; age 92. Dr Slanger was a 1925 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Gastroenterology. His memberships included the New York Academy of Gastroenterology, the New York State Society of Internal Medicine, the American Geriatrics Society, the Pan American Medical Association, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Louise E. Stauderman, MD, Kaneohe, Hawaii. Died March 1, 1991; age 93. Dr Stauderman was a 1919 graduate of

New York Medical College. She was a member of the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Fred Waldorf Stewart, MD, Sarasota, Florida. Died February 8, 1991; age 97. Dr Stewart was a 1924 graduate of Harvard Medical School, Boston. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Jerome Irving Tokars, MD, Palm Beach, Florida. Died March 25, 1991; age 70. Dr Tokars was a 1947 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Fellow of the American College of Chest Physicians. His memberships included the New York Academy of Medicine, the New York State Society of Internal Medicine, the American Society of Internal Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Joseph W. L. Trefz, MD, Union Springs. Died April 8, 1991; age 73. Dr Trefz was a 1953 graduate of Loma Linda University School of Medicine, Loma Linda-Los Angeles, California. He was a member of the Medical Society of the County of Cayuga and the Medical Society of the State of New York.

Carl Oswell Vrooman, MD, Scarsdale. Died April 6, 1991; age 89. Dr Vrooman was a 1928 graduate of Queens University, Faculty of Medicine, Kingston, Ontario, Canada. He was a Diplomate of the American Board of Ophthalmology. He was a member of the American Academy of Ophthalmology and Otolaryngology, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Lewis Whitehouse, MD, Brooklyn. Died April 11, 1991; age 77. Dr Whitehouse was a 1945 graduate of the University of London, Faculty of Medicine, England. He was a Fellow of the American Academy of Family Physicians. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media, and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1988; 88:456-462). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal's* particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 3,000 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 1,000 and 1,500 words. Other kinds of original essays should not exceed 2,500 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with *Système Internationale* (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

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The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear in the text. When there are three or fewer authors, all should be listed; where there are four or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Bowen J: Autoimmune paraneoplastic diseases of the nervous system. *NY State J Med* 1991; 91:2-3.
2. Cotran RS, Kumar V, Robbins SL: *Robbins Pathologic Basis of Disease*, ed 4. Philadelphia, WB Saunders Co, 1989, pp 842-845.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

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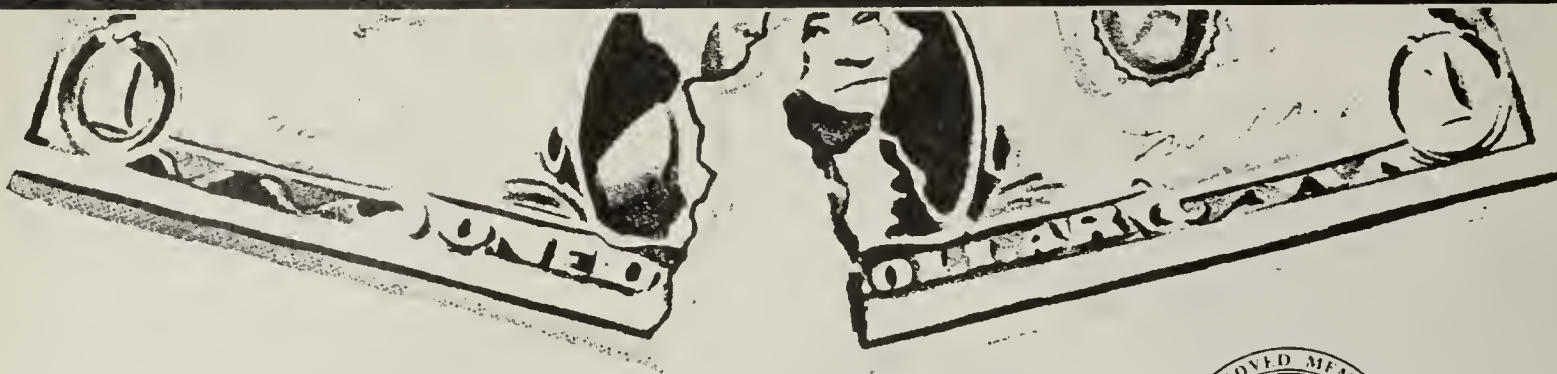


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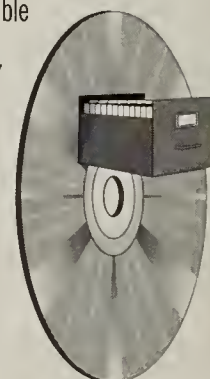
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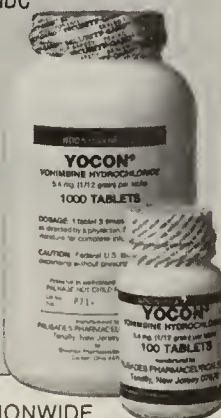
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1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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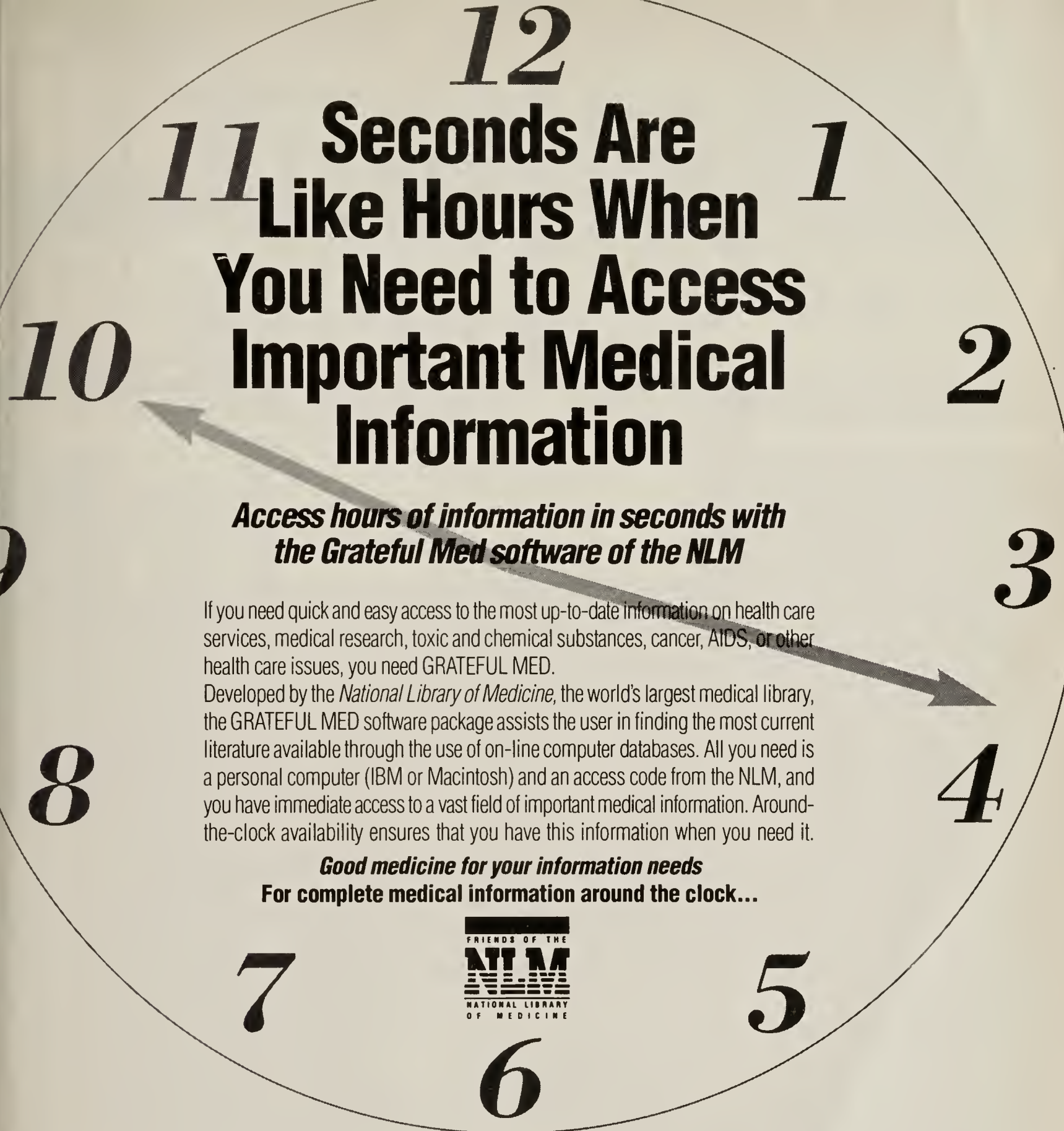
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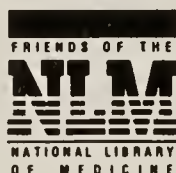


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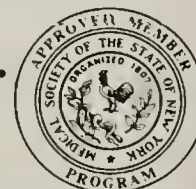
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SEPTEMBER 1991

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Sept 27-28. Radiation Oncology. Desmond Americana. Contact: Diane M. Martin, Office of Continuing Medical Education, Albany Medical College, 45 New Scotland Ave, Albany, NY 12208. Tel: (518) 445-5828.

COOPERSTOWN

Sept 25-27. Orthopaedic Conference. Otesaga Hotel. Contact: Charlotte L. Hoag, Medical Education Coordinator, Office of Medical Education, The Mary Imogene Bassett Hospital, One Atwell Rd, Cooperstown, NY 13326. Tel: (607) 547-3820.

MANHATTAN

Sept 21. Alumni Day 1991—Advances in Ocular Surgery. 5½ Cat I Credits. NYU Medical Center. Contact: NYU Medical Center, Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 263-5295.

Sept 20-21. Transvaginal Sonography: Office Use and Color Flow Applications. New York Hilton & Towers. Contact: Center for Continuing Education, College of Physicians & Surgeons of Columbia University, 630 W 168th St, New York, NY 10032. Tel: (212) 305-3682.

SOUTHAMPTON

Sept 6. Colon Cancer Screening. Southampton Hospital. Contact: Susan O'Rourke, CME Coordinator, Medical Staff Office, Southampton Hospital, 240 Meeting House Lane, Southampton, NY 11968.

AROUND THE NATION

CALIFORNIA

Sept 11-13. Seventh Annual Sonography Update Conference and Exhibit.

(continued on p 14A)

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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

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Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

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Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

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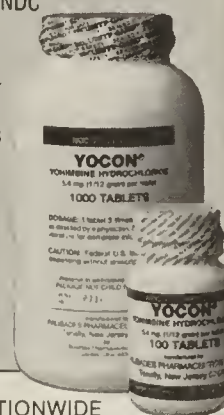
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Please see Brief Summary of Prescribing Information on adjacent page.

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Zantac[®] 150 Tablets
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Zantac[®] Syrup
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The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac[®] product labeling

INDICATIONS AND USAGE: Zantac[®] is indicated in

1 Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks

2 **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers

3 The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).

4 Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated

5 Treatment of **gastroesophageal reflux disease (GERD)**.

Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain

CONTRAINDICATIONS: Zantac[®] is contraindicated for patients known to have hypersensitivity to the drug

PRECAUTIONS: General: 1 Symptomatic response to Zantac[®] therapy does not preclude the presence of gastric malignancy 2 Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver

Laboratory Tests: False-positive tests for urine protein with Multistix[®] may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended

Drug Interactions: Although recommended doses of Zantac do not inhibit the action of cytochrome P-450 enzymes in the liver, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution)

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS: Headache, sometimes severe, seems to be related to Zantac[®] administration. Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and, rarely, pancreatitis have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, atrioventricular block, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred

Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported

Although controlled studies have shown no antiandrogenic activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine

OVERDOSSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac[®] product labeling)

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis

HOW SUPPLIED: Zantac[®] 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets

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Store between 15° and 30° C (59° and 86° F) in a dry place.

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September 1990

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COMMENTARIES

Rabies, raccoons, and suburbs

Rabies has long been enzootic in wildlife populations in the southeastern United States where raccoons have played a major role in its transmission.¹ Although a wildlife rabies epizootic began to move north in the early 1970s, it was the translocation of raccoons from enzootic areas in the southeastern United States that is linked to the epizootic that began in the mid-Atlantic region in 1977 and which has since spread into New York State and Connecticut. Infected raccoons were translocated north to supplement local populations hunted for sport. The numbers of these raccoons translocated by hunting clubs was substantial, totaling 2,300 alone in 15 eastern counties of Kentucky in 1975–1976.² Smith et al detected the first rabid raccoon in the epizootic in West Virginia in 1984. After their report, raccoon rabies was documented in Virginia, the District of Columbia, Maryland, and Pennsylvania. The rapid spread of this epizootic among raccoons is illustrated by the fact that Maryland, which had no known rabid raccoons prior to 1981, reported 735 in 1983.³ As of December 1987, 95 rabid raccoons had been reported within the city limits of Baltimore.⁴

In early May 1990, a rabid raccoon was shot by police in the daytime on the grounds of the Addison Central School in Steuben County, New York. Two months later a second rabid raccoon was identified in the same county. At that time, five rabid raccoons were found in Sullivan County. The first human exposure in New York State occurred on July 8, 1990, when a six-year old girl was attacked in the town of Delaware by a rabid raccoon. In April 1991, a rabid raccoon tenaciously chased a cyclist in Ridgefield, Connecticut.⁵ The large population of suburban raccoons coupled with the course of the current epizootic are predictive that rabies will appear in a number of suburbs in the next few years.

Contrary to what many assume, farmland and wilderness areas support lower densities of raccoons than suburban landscapes.⁶ Suburban and periurban areas provide abundant food sources in the form of garbage, and sewers and other isolated spots are excellent shelters. Not surprisingly, the spread of suburban developments into what was once farmland has frequently

resulted in the natural introduction of raccoons into areas where they were once unknown. A case in point familiar to this writer is southwestern Queens county, which until the early 1950s contained considerable farmland. Herman L. Brockmann, whose family farmed 50 acres along Cedar Lane between 1862 and 1953, does not recall that raccoons were ever present in this part of the county (personal communication, 1991). Yet, raccoons gradually moved into this area in the 1970s after it had become heavily suburbanized.

Terrestrial rabies has been absent in indigenous animals in New York City and many of its suburbs for several decades. Although dog bites are a serious problem in the city and surrounding areas, in recent decades there has been little concern about rabies.⁷ Although rabies has been consistently found in bats, human exposure is minimal. The spread of rabies in raccoons and other wildlife populations increases the risk of transmission to nonimmune domestic animals, especially dogs and cats, and through them to humans. Given these facts, both the New York City and New York State Departments of Health have strongly recommended the routine vaccination of both dogs and cats as have professional veterinary associations. In some jurisdictions, such as Westchester County, the vaccination of dogs and cats has been made mandatory.

Although the epizootic spread of rabies among raccoons is cause for concern, it should not lead to panic. From the epidemiologic perspective, rabies epizootics in these animals run a limited course of a few years, finally ending because of mortality rates and human interventions that reduce populations.^{3,6} In spite of this positive news, the disease can still linger and its rates increase as the raccoon population recovers over a period of time.

The primary prevention of rabies is fairly routine, but it consists of measures that many are apt to overlook. Although raccoons are primarily nocturnal, their interactions with domestic pets such as cats and dogs are fairly common. Thus, the regular vaccination of domestic pets not only protects them, but also prevents their transmitting the disease to humans. Transmission risks can also be reduced by not allowing pets to run loose, even in a

closed yard, since raccoons can easily breach most enclosures. Domestic pets should not be taken to enzootic areas where transmission risks are high. If they are taken into such areas, they should not be allowed outdoors unless leashed and under visual supervision. While in enzootic areas, individuals should not acquire domestic pets, unless there is documentation of rabies vaccination. The wisdom of this precaution was well illustrated by the case of a Manhattan couple who in 1990 brought back a stray kitten they found while vacationing in a rabies enzootic area in Pennsylvania. The kitten developed rabies, and some 10 individuals exposed to it then had to undergo post-exposure prophylaxis.⁸ Under no circumstances should individuals or their domestic pets have physical contact with wild animals, alive or dead, either at home or while away. In this regard, parents should make special efforts to warn children not to touch wild animals they may encounter. Rabies may render raccoons and other animals lethargic and easy to approach, thus increasing the risk of transmission. The day time appearance of usually nocturnal animals such as raccoons should raise suspicions that they may be rabid, and children should be informed never to approach them. Keeping wild animals as pets poses special risks since rabies vaccines are often ineffective in conferring immunity in some species.

The development of human diploid cell vaccines, a rabies vaccine adsorbed from rhesus lung diploid cell culture and human rabies immune globulin (HRIG) has greatly facilitated the postexposure management of patients.⁹ Postexposure prophylaxis is determined by a number of variables including the risk of rabies exposure in a given area, the type of exposure, the immunization status of the animal if known, and the results of an examination of the animal and/or its brain tissue. In determining an appropriate management plan, physicians should consult with their local health departments, which can advise whether or not treatment is necessary, provide guidance on how it is to be carried out, arrange for the examination of animal brain tissue and assist in

the close surveillance of domestic animals when available. In most instances both vaccine and HRIG must be administered as described in the special article in this issue of the *Journal*.¹⁰

As has been the case with a number of diseases, including tuberculosis and syphilis, rabies has re-emerged as a public health concern. This re-emergence requires the implementation of some fairly simple preventive measures long deemed unnecessary during the many-decades-long rabies-free era. The adoption of these measures coupled with the appropriate management of those exposed should prevent human deaths from rabies and minimize the anxiety and fear now present in many communities where rabid raccoons have been found.

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The etiology of retroperitoneal fibrosis

Although much has been learned about retroperitoneal fibrosis (RF) since it was first described in 1905, concepts regarding this enigmatic disease are still evolving. Large series of patients have now been gathered and the cumulative clinical experience with RF has been summarized in several excellent reviews.¹⁻⁶ Research efforts are now concentrated on more clearly delineating the pathophysiology of RF. This commentary briefly reviews the salient features of RF and discusses evidence that favors an immune basis for the idiopathic form of the disease.

RF is characterized by the development of a fibrotic mass that surrounds the abdominal aorta and its branches. Histologic examination reveals a spectrum of inflammatory activity. Specimens obtained early in the

course of the disease contain collagen bundles that surround large areas of lymphocytes, plasma cells, and fibroblasts. Specimens obtained later on are for the most part acellular and avascular with calcium deposits scattered throughout.⁷ When the fibrosis is extensive, local structures such as the ureters can become obstructed.

An uncommon disorder, RF has an incidence that has variably been estimated at 1 case per 25,000 hospital admissions⁵ and 2 cases per 1 million population per year.⁸ Males are affected two to three times more often than females, and patients are usually diagnosed in the fourth through seventh decades of life. The most common symptom is dull, noncolicky flank or back pain. Patients may also complain of malaise, fever, anorexia,

or symptoms related to obstruction of retroperitoneal structures. The majority of patients are hypertensive, but the physical examination findings are otherwise variable. Only about 10% of patients have a palpable abdominal mass. Routine laboratory results are similarly nonspecific and can be related to the organ systems involved in the fibrotic process. An elevated blood urea nitrogen, an elevated erythrocyte sedimentation rate (ESR), and anemia are common.^{1,2,4}

The patient's history, physical examination, and laboratory findings should be carefully scrutinized to determine whether they contain any factor that has been proposed as etiologic for RF. This is usually a fruitless search as the vast majority of patients with RF are believed to have idiopathic disease. In only less than one third of cases can an etiologic factor be identified.¹ Fibrosis in the retroperitoneum can develop in the presence of malignancies such as lymphomas, Hodgkin's disease, and solid tumors.^{1,9} Fibrosis can surround an abdominal aortic aneurysm (termed "inflammatory aneurysms") or occur in response to retroperitoneal infection, trauma, or foreign bodies. A great deal of attention has been focused on drug-induced RF, and although many drugs have been implicated as casual, convincing evidence exists only for the ergot preparation, methysergide. Beta blockers, large doses of analgesics, and various antihypertensives have also been proposed, but supporting data are anecdotal and usually in the form of isolated case reports.^{5,6}

Once a diagnosis of RF is suspected on clinical grounds, the presence of a retroperitoneal mass must be confirmed by imaging studies. Although the older literature stresses the importance of intravenous pyelography, ultrasound and computer tomography scans are safer and more reliable diagnostic tools.⁵ Experience with magnetic resonance (MR) imagers is limited but promising.^{10,11} Early reports indicate that MR studies may be sophisticated enough to differentiate noninvasively between malignancy-related and benign, idiopathic RF.¹²

The possible presence of malignancy is an important concern and has led some to advocate that most, if not all, patients with RF should have a laparotomy for histologic examination of deep biopsy specimens.^{4,13} This now seems to be an overly aggressive approach since certain subgroups of patients, such as those with drug-related RF or inflammatory aneurysms, do well with conservative, nonsurgical management. Many patients with malignant RF have a prior history of cancer, and newer imaging studies can usually give an indication whether or not a malignancy is present. These factors may help decide whether or not laparotomy is necessary.⁶

Surgery is required in patients who have evidence of actual or impending obstructive complications, the most common of which is ureteral obstruction. The surgical procedure of choice in this situation is to free the ureters from the fibrotic mass, place them in a lateral position away from the fibrosis, and wrap them in a protective layer of omentum.^{4,14} When there is evidence of retained renal function before surgery, the results of surgery plus medical therapy are excellent. When a kidney is nonfunc-

tional preoperatively, the chances for a return of function are small.⁴

Most patients with RF have the idiopathic form of the disease. A growing body of literature suggests that fibrosis occurs in these patients as a result of a systemic inflammatory or autoimmune process. Cases have been reported in which idiopathic RF coexisted with immune-mediated diseases such as systemic lupus erythematosus¹⁵ and polyarteritis nodosa.¹⁶ Approximately 10–15% of patients with RF have additional fibrosis outside of the abdomen. This fibrosis can be widespread and involve several organ systems, including the thyroid and heart. Elevated γ -globulin fractions and positive autoantibody screens have also been reported in RF patients.^{1,4,5} Perhaps the most important indirect evidence favoring an immune basis for idiopathic RF is the impressive response of most patients to immunosuppressive therapy.

Ross and Tinkler first reported the use of corticosteroids as an adjunct to surgical therapy for RF in the late 1950s,¹⁷ and considerable experience has accumulated since then to support their use. Surgical therapy will alleviate fibrotic obstruction but, if idiopathic RF is truly an immune-mediated disease, surgery alone cannot be expected to prevent recurrence or progression of the inflammatory process. Adding corticosteroids postoperatively appears to both improve surgical outcome and decrease the risk of recurrent ureteral obstruction.^{4,6} Patients treated with surgery plus corticosteroids have experienced resolution of systemic symptoms, a rise in hemoglobin, a fall in ESR, and elimination of autoantibodies.⁵ Occasional patients, usually those who are unable or unwilling to undergo surgery, have been treated with immunosuppression alone with favorable results.^{4,5,6} In selecting patients for immunosuppression therapy, it is important to note that patients in the early, inflammatory stage of RF respond better than those in the late, fibrotic stage.¹⁸

Given that there is ample indirect evidence supporting the concept of idiopathic RF as an immune-mediated disease, the question remains as to the antigen(s) against which the inflammation is directed. Histologic analysis reveals that inflammation only occurs adjacent to areas of the abdominal aorta where atherosclerotic plaques have developed and the vascular media has been thinned or breached.^{3,7} Hence, the term "chronic periaortitis" has been proposed as a better descriptive name for the disorder than retroperitoneal fibrosis. This histologic pattern led to the suggestion that the inciting antigen was located in the atherosclerotic plaque itself. Mitchinson and colleagues proposed that the antigen remains sequestered in the plaque until the vascular media is breached; the antigen is then exposed to the circulation, antibodies are produced, and the inflammatory process begins.³ This theory appeared to gain credence when antibodies, mostly immunoglobulin G and directed against ceroid, were subsequently demonstrated near atherosclerotic plaques that had developed in association with thinned vascular media.¹⁹

Ceroid is an insoluble polymer of oxidized lipid and protein. It is found in all atherosclerotic plaques and is thought to be produced by macrophage foam cells

located in the base of the plaque. Parums et al have examined sera from a variety of patient subgroups for antibodies to ceroid and other lipid degradation products. Antibodies to ceroid and oxidized low-density lipoprotein were found in all 20 patients they studied with idiopathic RF (12 patients had RF associated with an inflammatory aneurysm, and 8 had RF with no aneurysm). An additional 20 patients with severe periaortic inflammation discovered incidentally at autopsy were studied, and 17 had antibody to ceroid. When 20 young, healthy, volunteers were studied, none had antibodies to ceroid in their sera. This appeared to be a highly significant result. However, further investigation by the same authors showed positive antibody screens for anticeroid antibodies in 50% of healthy, elderly patients and 50% of patients with documented atherosclerotic heart disease; none of these patients had RF.²⁰ Clearly, causality for anticeroid antibodies has not been proven, and it may be that some other factor, in addition to the antibody response, is responsible for the inflammatory response.

In this issue of the *Journal*, Maguire et al present a patient previously exposed to asbestos who developed rapidly progressive pleural and retroperitoneal fibrosis.²¹ The authors suggest that this may be the first reported case of RF induced by asbestos. The ability of asbestos to produce fibrosis in the thorax is certainly well documented and, as the authors point out, asbestos bodies have been found in retroperitoneal organs.²² However, several questions must be addressed before an association between asbestos and RF can be definitely accepted.

Although the patient had a history of significant asbestos exposure, no asbestos bodies were reported in the histologic descriptions of biopsy specimens. Stronger evidence for an association would have been provided by the presence of asbestos bodies in or around the fibrotic tissue. Given the millions of patients worldwide who suffer from asbestos-induced pleuropulmonary disease, one might assume that if asbestos were truly associated with RF, other cases such as this would have already been identified. Could there be a reason other than that of asbestos exposure to explain the pleural and retroperitoneal fibrosis in the patient presented? The patient had documented atherosclerotic heart disease and, if the data of Parum et al can be applied to others, he could possibly have had anticeroid antibodies. The asbestos exposure may be a "red herring" and this report may actually be one of idiopathic RF due to ceroid-induced inflammation. Pleural fibrosis would not be expected in a patient with idiopathic RF, but extensive pleural fibrosis has been reported in at least one case of ergot-related RF.²³ Because of these concerns, more investigation is needed before asbestos can be considered etiologic. At this point, it is probably best to add asbestos to the long list of factors that may be associated

with but have not been proven to cause retroperitoneal fibrosis.

One final point of interest is the apparent absence of a description of RF prior to 1905. Was RF simply overlooked because of its rarity or is RF a disease of the 20th century? If one accepts that ceroid is immunogenic and that antibodies to it are causal, an answer to this question can be suggested. RF is usually diagnosed after the age of 30, and it may require the presence of extensive atherosclerosis to develop. It is possible that increased life expectancy and the high incidence of atherosclerosis present in industrialized Western society have contributed to the recent emergence of RF. This is of course highly speculative but, if true, we can expect to see a greater number of patients with RF in the future.

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An urban primary school health program

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ABSTRACT. This paper summarizes the results of the first three years of an integrated on-site school health demonstration project based on the family practice model of delivering primary health care. An inner city public elementary school was chosen as the study location. Of the 712 study participants, 98% were black or Hispanic. Prior to implementation of the demonstration project, the Health Guarded Index for the study population was computed to be 58%. Among study participants, this index rose to 79% during the first year of the project and eventually reached 95% during the third year of the project. The absentee rates among study participants relative to nonparticipants decreased to 8.7% during the first year of the project and by 36.2% during the third year of the project. The substantial increase in the Health Guarded Index indicates that, among study participants, preventable defects, such as lack of immunizations, dental care, screening for common problems, and follow-up had been largely corrected. The substantial decline in absenteeism among study participants clearly shows the effectiveness of the demonstration project in promoting good health by decreasing morbidity and/or decreasing recovery time. Overall, the results of the three-year demonstration project reported here show that a carefully designed, well-coordinated school health program based on a family practice model can have a substantially favorable impact on the health of participating children.

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For children living in deprived areas of large cities, quality health care has traditionally been inadequate and difficult to obtain. Such problems as fragmented health services, poverty, inadequate housing, overcrowding, unemployment, lack of education, and environmental hazards are associated with increased health risks (eg, tuberculosis, lead poisoning, respiratory illness, parasitosis, anemia, malnutrition, inadequate immunizations, and psychosocial problems).¹⁻³ During the 1960s and 1970s, programs such as Head Start, Medicaid, community health centers, and the maternal and child

health program were implemented under Title V of the Social Security Act. However, the impact of these programs during the late 1970s and 1980s has been significantly reduced because of inflation, restricted eligibility criteria, cutbacks in funding, and an increase in the number of poor immigrant families with children.⁴⁻⁶ In addition, multiple sites of care in the form of specialty clinics and emergency rooms are often the missed opportunity for a regular source of child health care from a primary care practitioner.^{7,8}

An on-site integrated school health program represents a potential solution to the health needs of children, because it can offer care that is easily accessible and affordable and provides a link to home and community support services.^{9,10} Nevertheless, many such programs, particularly in New York City, consist of poorly staffed and equipped clinics that provide a minimum of care and are dominated by poorly coordinated triage and referral systems.^{11,12} Primary health care in the school environment can achieve a level of care that is accountable, coordinated, continuous, and comprehensive.¹³ This study presents the results of an on-site school health demonstration project based on a family practice model that was designed to upgrade the level of health and well being of students attending an inner city public elementary school.

METHODS

A public elementary school located in the East New York section of Brooklyn, one of New York City's five boroughs, was chosen as the project location. The East New York section of Brooklyn is an area rated as having the highest degree of health needs by the Health Systems Agency. This community also qualifies as both a medically underserved area and a health manpower shortage area.¹⁴ By using this school, we hoped to assess the impact of such a project in a population most in need of primary care.

The potential study population consisted of 1,250 children in grades pre-kindergarten through six. All children and their families were invited to participate in the demonstration project. Although a comprehensive evaluation was recommended on an elective basis, children could enter the program via an initial acute care visit. Thereafter, an appointment was made for a complete evaluation. On entry, the following information was obtained from the patient and one or more family members: family and prenatal history, review of systems, history of the current illness, history of growth and development, and information pertaining to current or prior medication use. In addition, the following demographic data were collected: family income, present or absence of health insurance, number of persons per residential room, number of children at home, education level of father or mother, and the

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employment history of mother and/or father. A Spanish speaking assistant was available for interpretation during all interviews.

The initial physical examination consisted of vital signs, anthropometric data, a thorough examination of all body systems, and appropriate laboratory investigations. Evaluations were concluded with diagnosis(es), disposition, and further recommendations (ie, referrals, consultations, diet, and exercise). The evaluation for an episodic visit concentrated on the specific problem area(s). Care was delivered by a team consisting of a project director, nurse practitioner, two health technicians, a part-time clerical assistant, rotating family practice residents, and medical and nurse practitioner students. The project director, a family physician, oversaw the program on a regular basis and made weekly clinical rounds with the health care providers. The demonstration project's school health office was open five days a week during the school year and two days a week during holiday and vacation periods (summers). Emergency coverage was available through the 24-hour on-call system of the Department of Family Practice, State University of New York Health Science Center at Brooklyn. The demonstration project was carried out over the three-year period from January 1986 through January 1989.

Prior to entry onto the computer, all data forms were reviewed for consistency and accuracy by the project team's health technicians. A data base was then established using the rational data base management program, Rbase 5000, on an IBM PC desktop computer. Separate data files were kept for consultations, referrals, and absences from school. A Health Guarded Index was computed for each study year and the year preceding the start of the project.¹⁵ This index measures preventable problems that are prevented and correctable problems that are corrected. Preventable problems mean that the child's immunization status must be equal to the state requirements for school entry. Correctable problems refer to hearing and vision defects that are identified by routine screening and are corrected within six months of the date of the initial referral.

Absentee rates for project participants and nonparticipants were compiled during each of the three study years to assess the effectiveness of the demonstration project with regard to decreased morbidity and/or shorter recovery periods. All diagnoses were coded according to ICD-9-CM classifications before entry onto the computer. Statistical analyses of the data were as follows: continuous data were analyzed using tests or the Pearson correlation coefficient where appropriate, and categorical data were analyzed by χ^2 analysis using Yates correction for continuity.

RESULTS

A total of 712 students and their families were registered with the project. Of the children, 98% were either black (46.4%) or Hispanic (51.5%). The average student was 9.6 ± 1.4 years old. Of the children, 52% were female, and 48% were male. The reported modal per capita income (PCI) category was \$6,000–8,000 per year. Of the families, 31% had no form of health insurance, and 70% had no regular source of medical or dental care. Of the 69% with health insurance, 52% had Medicaid, whereas 17% had a private carrier. Of the homes, 81% had one or more structural, faulty plumbing or heating, or functional problems (eg, peeling paint, lack of security, damaged walls). The average number of persons per home was three. Both fathers and mothers had achieved the same mean educational level, although the variability was greater for fathers (11 ± 1.2 year for mothers vs 11 ± 2.4 year for fathers). Although fewer mothers were employed (54% vs 71%), more held skilled jobs when compared with fathers (12% vs 6%) ($p < 0.05$).

All 712 children enrolled in the project were given a comprehensive history and physical examination. A total of 3,487 visits were made to the school health office, representing 1.6 visits/student/year. Of those visiting the school health office, 49.5% were females and 50.5% were males. A total of 6,525 diagnoses were made, representing 1.9 diagnoses/visit. Of the diagnoses, 53% involved females, and 47% involved males. Diagnoses by general ICD-9-CM classification are shown in Table I. Thirty-five percent of all

TABLE I. Number of Diagnoses by ICD-9-CM Classification for Project Participants (1986–1989)

Diagnoses	No.	Percentage
Infectious and parasitic disease	373	5.7
Neoplasms	7	0.1
Endocrine, nutrition, and metabolic disease	218	3.3
Blood and immune disease	142	2.2
Mental health disease	197	3
Nervous system disease	812	12.4
Circulatory disease	23	0.4
Respiratory disease	555	8.5
Digestive disease	280	4.3
Genitourinary disease	19	1.8
Skin disease	308	4.7
Musculoskeletal disease	75	1.2
Congenital disease	5	0.1
Symptoms, signs	604	9.3
Injury/poisoning	546	8.4
Supplementary (V&E codes)	2,260	34.6
Total	6,525	100

diagnoses consisted of disorders of the respiratory and nervous systems, infectious and parasitic diseases, and all deferred symptoms and signs (Table I). An additional 35% of all diagnoses included the most common factors influencing health status and contact with health services (ie, immunizations, routine health checks, screenings) (V codes) and external causes of injury and poisoning (E codes) (Table I). Table II shows, in more detail, the 20 most common clinical diagnoses, excluding the supplementary (V and E) codes. As shown in Table II, the four major diagnoses were acute respiratory infections, abrasions/friction burns, nonspecific viral infections, and obesity. These diagnoses accounted for almost 13% of all visits.

Six hundred and four referrals were made, and 536 (89%) were completed with follow-up. Incomplete referrals occurred most frequently for ophthalmologic (52%) and dental problems (36%). The average number of referrals per child was 1.3. Three hundred and forty-nine children (47%) demonstrated evidence on one or more occasions of new morbidity, with almost 46% of the group

TABLE II. The 20 Most Common Diagnoses for Project Participants (1986–1989)

Diagnoses	No.	Percentage
Acute upper respiratory infection NOS*	258	4.0
Obesity	201	3.1
Superficial injury	188	2.9
Viral infection NOS*	180	2.8
Visual discomfort	153	2.3
Otitis media NOS*	143	2.2
Dermatitis NOS*	131	2.0
Impacted cerumen	118	1.8
Asthma NOS*	113	1.7
Sprain/strain NOS*	107	1.6
Disorders of refraction and accommodation	102	1.6
Contusion of face, scalp, neck	97	1.5
Dental caries	95	1.5
Abdominal pain	94	1.4
Family dysfunction	88	1.3
Conjunctivitis	80	1.2
Hematuria	79	1.2
Hearing loss	76	1.2
Cardiac murmur NOS*	76	1.2
Proteinuria	75	1.1
Total	2,454	37.6

*NOS indicates not otherwise specified.

TABLE III. Absenteeism Rates for Participants vs Nonparticipants

	Absenteeism Rates (Days/child/year)		
	1986	1987	1988
Participants	12.98	10.39	8.47
Nonparticipants	14.22	15.46	13.28
Percentage decline	8.72%*	32.79%†	36.22%†

* $p < 0.05$

† $p < 0.01$

exhibiting problems related to the home environment and family. There were five cases of child abuse, all of which had a positive outcome without removing the child from the family. Two hundred and fifty-eight children (36%) required immunization updates: 93 required more than one immunization, and 15 required all primary vaccinations. There were eight positive responses to purified protein derivative on tuberculin test, one case of lead poisoning, and one case of malnutrition.

Patients on Medicaid had significantly more diagnoses per visit than did patients with private insurance (1.7 vs 1.4 respectively, $p < 0.01$). Private insurance correlated with increased visit rates ($r = 0.16$, $p < 0.01$) and fewer diagnoses ($r = -0.13$, $p < 0.05$).

The Health Guarded Index rose to 79% during the first year of the program and to 89% and 95% the second and third years of the program, respectively. Considering that this index was computed to be 58% before initiation of the demonstration project, this is strong evidence that the project significantly improved the health and well being of the children who participated. Moreover, Table III shows the effect of the demonstration project on the absentee rates of the children enrolled. Absenteeism rates for project participants were significantly lower than those for nonparticipants in each of the years studied. The difference in absentee rates between participants vs nonparticipants rose from 8.72% during the project's first year to 36.22% in the third year of the project (Table III). This clearly shows the effectiveness of the demonstration project in promoting good health via decreasing morbidity and/or decreasing recovery time.

DISCUSSION

The results of this three-year study indicates that a carefully designed, well-coordinated school health program based on a family practice model can have a substantially favorable impact on the health of the participating children. Tangible measures of success include substantial reduction in absenteeism and substantial improvement in the Health Guarded Index for study participants.

It was somewhat surprising to find that at the beginning of this study, 42% of the children required one or more preventive and/or corrective health measures. Similar recent investigations have shown rates of 15% to 30%.^{11,12,15} Failure to screen for dental, hearing, and vision defects, absence of follow-up when such abnormalities were detected, and lack of immunization follow-up were the major factors responsible for this large percentage of study participants in need of health care on entry into this study. This observation, together with the fact that the demonstration project reduced these problems to approximately 5% of those enrolled, underscores the need for well-coordinated school health care programs, and in particular, the need for meticulous identification and follow-up procedures. Similarly, the immunization

delay rate of 36% observed at the start of this project was reduced to 1% during the study period.

There were several diagnostic categories with unexpected frequency distributions. Growth and development disorders, particularly delayed development, constituted 1.1% of all diagnoses and were four times more frequent than indicated by the general pediatric survey conducted by Poole et al.¹⁶ Anemia ($n = 43$), lead poisoning ($n = 1$), and malnutrition ($n = 1$) were uncommon diagnoses. These findings are in contrast to those reported by similar studies dealing with similar populations^{11,17-19} and have important implications regarding the New York City Task Force on School Health Report of 1984, which recommended the dropping of routine hemocrit, urine analysis, and lead-level screening in school age children. Future research will be required to substantiate our findings and to define future screening strategies.

This study demonstrates the effectiveness of a well designed and coordinated school health program. The multidisciplinary team approach used in this study has highlighted the valuable role of the nurse practitioner, optimized the use of physician time, and promoted the education of future doctors and nurses. As such, the school health program reported herein should provide a model for future school health programs.

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Rabies prevention in the United States, 1991: Recommendations of the Immunization Practices Advisory Committee*

Following the marked decrease of rabies cases among domestic animals in the United States in the 1940s and 1950s, indigenously acquired rabies among humans decreased to fewer than two cases per year in the 1960s and 1970s and fewer than one case per year during the 1980s.¹ In 1950, for example, 4,979 cases of rabies were reported among dogs and 18 were reported among human populations; in 1989, 160 cases were reported among dogs and one was reported among humans. Thus, the likelihood of human exposure to a rabid domestic animal has decreased greatly; however, the many possible exposures that result from frequent contact between domestic dogs and humans continue to be the basis of most antirabies treatments.²

Rabies among wild animals—especially skunks, raccoons, and bats—has become more prevalent since the 1950s, accounting for >85% of all reported cases of animal rabies every year since 1976.¹ Rabies among animals occurs throughout the continental United States; only Hawaii remains consistently rabies-free. Wild animals now constitute the most important potential source of infection for both humans and domestic animals in the United States. In much of the rest of the world, including most of Asia, Africa, and Latin America, the dog remains the major species with rabies and the major source of rabies among humans. Of the 13 human rabies deaths reported to CDC from 1980 through 1990, 9 appear to have been related to exposure to rabid animals outside of the United States.³⁻⁹

Although rabies among humans is rare in the United States, every year approximately 18,000 persons receive rabies preexposure prophylaxis and an additional 10,000 receive postexposure prophylaxis. Appropriate management of persons possibly exposed to rabies depends on the interpretation of the risk of infection. Decisions about management must be made immediately. All available methods of systemic prophylactic treatment are complicated by occasional adverse reactions, but these are rarely severe.¹⁰⁻¹⁴

Data on the efficacy of active and passive rabies immunization have come from both human and animal studies.

Evidence from laboratory and field experience in many areas of the world indicates that postexposure prophylaxis combining local wound treatment, passive immunization, and vaccination is uniformly effective when appropriately applied.¹⁵⁻²⁰ However, rabies has occasionally developed among humans when key elements of the rabies postexposure prophylaxis treatment regimens were omitted or incorrectly administered (see Postexposure Treatment Outside the United States).

RABIES IMMUNIZING PRODUCTS

There are two types of rabies immunizing products.

1. Rabies vaccines induce an active immune response that includes the production of neutralizing antibodies. This antibody response requires approximately 7-10 days to develop and usually persists for ≥ 2 years.
2. Rabies immune globulins (RIG) provide rapid, passive immune protection that persists for only a short time (half-life of approximately 21 days).^{21,22}

In almost all postexposure prophylaxis regimens, both products should be used concurrently.

Vaccines Licensed for Use in the United States. Two inactivated rabies vaccines are currently licensed for preexposure and postexposure prophylaxis in the United States. Human diploid cell vaccine (HDCV) is prepared from the Pitman-Moore strain of rabies virus grown in MRC-5 human diploid cell culture and concentrated by ultrafiltration.²³ The vaccine is inactivated with betapropiolactone¹⁸ and is supplied in the following forms:

1. Intramuscular (IM) administration, a single-dose vial containing lyophilized vaccine (Pasteur-Merieux Serum et Vaccins, Imovax® Rabies, distributed by Connaught Laboratories, Inc., Phone: 800-VACCINE) that is reconstituted in the vial with the accompanying diluent to a final volume of 1.0 mL just before administration.
2. Intradermal (ID) administration, a single-dose syringe containing lyophilized vaccine (Pasteur-Merieux Serum et Vaccins, Imovax® Rabies ID, distributed by Connaught Laboratories, Inc.) that is reconstituted in the syringe to a volume of 0.1 mL just before administration.²⁴

A human diploid-cell-derived rabies vaccine developed in the United States (Wyeth Laboratories, Wyvac®) was

* These guidelines are reprinted from *Morbidity and Mortality Weekly Report*, 1991; 40:1-19.

For assistance with problems or questions about rabies prophylaxis, contact your local or state health department. If local or state health department personnel are unavailable, call the Division of Viral and Rickettsial Diseases, Center for Infectious Diseases, CDC ([404] 639-1075 during working hours or [404] 639-2888 nights, weekends, and holidays).

recalled by the manufacturer from the market in 1985 and is no longer available.²⁵

Rabies Vaccine Adsorbed (RVA) (Michigan Department of Public Health) was licensed on March 19, 1988; it was developed and is currently distributed by the Biologics Products Program, Michigan Department of Public Health. The vaccine is prepared from the Kissling strain of Challenge Virus Standard rabies virus adapted to fetal rhesus lung diploid cell culture.²⁶⁻³² The vaccine virus is inactivated with betapropiolactone and concentrated by adsorption to aluminum phosphate. Because RVA is adsorbed to aluminum phosphate, it is liquid rather than lyophilized. RVA is currently available only from the Biologics Products Program, Michigan Department of Public Health (Phone: [517] 335-8050).

Both types of rabies vaccines are considered equally efficacious and safe when used as indicated. The full 1.0-mL dose of either product can be used for both preexposure and postexposure prophylaxis. Only the Imovax® Rabies ID vaccine (HDCV) has been evaluated by the ID dose/route for preexposure vaccination³³⁻³⁶; the antibody response and side effects after ID administration of RVA have not been studied.²⁴ *Therefore, RVA should not be used intradermally.*

RIGs Licensed for Use in the United States. HRIG (Cutter Biological [a division of Miles Inc.], Hyperab®; and Pasteur-Merieux Sérum et Vaccins, Imogam® Rabies, distributed by Connaught Laboratories, Inc.) is an antirabies gamma globulin concentrated by cold ethanol fractionation from plasma of hyperimmunized human donors. Rabies neutralizing antibody content, standardized to contain 150 international units (IU) per mL, is supplied in 2-mL (300 IU) and 10-mL (1,500 IU) vials for pediatric and adult use, respectively. Both HRIG preparations are considered equally efficacious and safe when used as described in this document.

POSTEXPOSURE PROPHYLAXIS: RATIONALE FOR TREATMENT

Physicians should evaluate each possible exposure to rabies and if necessary consult with local or state public health officials regarding the need for rabies prophylaxis (Table I). In the United States, the following factors should be considered before specific antirabies treatment is initiated.

Types of Exposure. Rabies is transmitted only when the virus is introduced into open cuts or wounds in skin or mucous membranes. If there has been no exposure (as described in this section), postexposure treatment is not necessary. The likelihood of rabies infection varies with the nature and extent of exposure. Two categories of exposure (bite and nonbite) should be considered.

Any penetration of the skin by teeth constitutes a bite exposure. Bites to the face and hands carry the highest risk, but the site of the bite should not influence the decision to begin treatment.¹⁷

Scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material (such as brain tissue) from a rabid animal constitute nonbite exposures. If the material containing the virus is dry, the virus can be considered noninfectious.

TABLE I. Rabies Postexposure Prophylaxis Guide, United States, 1991

Animal Type	Evaluation and Disposition of Animal	Postexposure Prophylaxis Recommendations
Dogs and cats	Healthy and available for 10-d observation	Should not begin prophylaxis unless animal develops symptoms of rabies*
	Rabid or suspected rabid	Immediate vaccination
	Unknown (escaped)	Consult public health officials
Skunks, raccoons, bats, foxes, and most other carnivores; woodchucks	Regarded as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests†	Immediate vaccination
Livestock, rodents, and lagomorphs (rabbits and hares)	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares almost never require antirabies treatment

* During the 10-d holding period, begin treatment with HRIG and HDCV or RVA at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.

† The animal should be killed and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.

Other contact by itself, such as petting a rabid animal and contact with the blood, urine, or feces (eg, guano) of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis.

Although occasional reports of transmission by nonbite exposure suggest that such exposures constitute sufficient reason to initiate postexposure prophylaxis under some circumstances, nonbite exposures rarely cause rabies.³⁷ The nonbite exposures of highest risk appear to be exposures to large amounts of aerosolized rabies virus, organs (ie, corneas) transplanted from patients who died of rabies, and scratches by rabid animals. Two cases of rabies have been attributed to airborne exposures in laboratories, and two cases of rabies have been attributed to probable airborne exposures in a bat-infested cave in Texas.^{38,39}

The only documented cases of rabies caused by human-to-human transmission occurred among six recipients of transplanted corneas. Investigations revealed each of the donors had died of an illness compatible with or proven to be rabies.⁴⁰⁻⁴³ The six cases occurred in four countries: Thailand (two cases), India (two cases), the United States (one case), and France (one case). Stringent guidelines for acceptance of donor corneas have reduced this risk.

Apart from corneal transplants, bite and nonbite exposures inflicted by infected humans could theoretically transmit rabies, but no such cases have been documented.⁴⁴ Adherence to respiratory precautions will minimize the risk of airborne exposure.⁴⁵

Animal Rabies Epidemiology and Evaluation of Involved Species. Carnivorous wild animals (especially skunks, raccoons, and foxes) and bats are the animals most often infected with rabies and the cause of most indigenous cases of human rabies in the United States since 1960.¹ All bites by wild carnivores and bats must be considered possible exposures to the disease. Postexposure prophylaxis should be initiated when patients are exposed to wild carnivores unless (1) the exposure occurred in a part of the continental United States known to be free of terrestrial rabies and the results of immunofluorescence antibody testing will be available within 48 hours or (2) the animal has already been tested and shown not to be rabid. If treatment has been initiated and subsequent immunofluorescence testing shows that the exposing animal was not rabid, treatment can be discontinued.

Signs of rabies among carnivorous wild animals cannot be interpreted reliably; therefore, any such animal that bites or scratches a person should be killed at once (without unnecessary damage to the head) and the brain submitted for rabies testing. If the results of testing are negative by immunofluorescence, the saliva can be assumed to contain no virus, and the person bitten does not require treatment.

If the biting animal is a particularly rare or valuable specimen and the risk of rabies small, public health authorities may choose to administer postexposure treatment to the bite victim in lieu of killing the animal for rabies testing.⁴⁶ Such animals should be quarantined for 30 days.

Rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are almost never found to be infected with rabies and have not been known to cause rabies among humans in the United States. However, from 1971 through 1988, woodchucks accounted for 70% of the 179 cases of rabies among rodents reported to CDC.⁴⁷ In all cases involving rodents, the state or local health department should be consulted before a decision is made to initiate postexposure antirabies prophylaxis.

Exotic pets (including ferrets) and domestic animals crossbred with wild animals are considered wild animals by the National Association of State Public Health Veterinarians and the Conference of State and Territorial Epidemiologists because they may be highly susceptible to rabies and could transmit the disease. Because the period of rabies virus shedding in these animals is unknown, these animals should be killed and tested rather than confined and observed when they bite humans.⁴⁶ Wild animals (skunks, raccoons, and bats) and wild animals crossbred with dogs should not be kept as pets.⁴⁶

The likelihood that a domestic animal is infected with rabies varies by region; hence, the need for postexposure prophylaxis also varies. In the continental United States, rabies among dogs is reported most commonly along the US-Mexico border and sporadically from the areas of the United States with enzootic wildlife rabies, especially the Midwest. During most of the 1980s in the United States, more cats than dogs were reported rabid; the majority of these cases were associated with the mid-Atlantic epizootic of rabies among raccoons. The large number of rabies-infected cats may be attributed to fewer cat vaccination

laws, fewer leash laws, and the roaming habits of cats. Cattle tend to be most often exposed to rabies via rabid skunks.

In areas where canine rabies is not enzootic (including virtually all of the United States and its territories), a healthy domestic dog or cat that bites a person should be confined and observed for 10 days. Any illness in the animal during confinement or before release should be evaluated by a veterinarian and reported immediately to the local health department. If signs suggestive of rabies develop, the animal should be humanely killed and its head removed and shipped, under refrigeration, for examination by a qualified laboratory. Any stray or unwanted dog or cat that bites a person should be killed immediately and the head submitted as described for rabies examination.⁴⁶

In most developing countries of Asia, Africa, and Central and South America, dogs are the major vector of rabies; exposures to dogs in such countries represent a special threat. Travelers to these countries should be aware that more than 50% of the rabies cases among humans in the United States result from exposure to dogs outside the United States. Although dogs are the main reservoir of rabies in these countries, the epizootiology of the disease among animals differs sufficiently by region or country to warrant the evaluation of all animal bites.

Exposures to dogs in canine rabies-enzootic areas outside the United States carry a high risk; some authorities therefore recommend that postexposure rabies treatment be initiated immediately after such exposures. Treatment can be discontinued if the dog or cat remains healthy during the 10-day observation period.

Circumstances of Biting Incident and Vaccination Status of Exposing Animal. An unprovoked attack by a domestic animal is more likely than a provoked attack to indicate that the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as provoked.

A fully vaccinated dog or cat is unlikely to become infected with rabies, although rare cases have been reported.⁴⁸ In a nationwide study of rabies among dogs and cats in 1988, only one dog and two cats that were vaccinated contracted rabies.⁴⁹ All three of these animals had received only single doses of vaccine; no documented vaccine failures occurred among dogs or cats that had received two vaccinations.

POSTEXPOSURE PROPHYLAXIS: LOCAL TREATMENT OF WOUNDS AND VACCINATION

The essential components of rabies postexposure prophylaxis are local wound treatment and the administration, in most instances, of both HRIG and vaccine (Table II). Persons who have been bitten by animals suspected or proven rabid should begin treatment within 24 hours. However, there have been instances when the decision to begin treatment was not made until many months after the exposure because of a delay in recognition that an exposure had occurred and awareness that incubation periods of more than one year have been reported.

In 1977, the World Health Organization (WHO) recommended a regimen of RIG and six doses of HDCV over a 90-day period. This recommendation was based on studies in Germany and Iran.^{16,20} When used this way, the

TABLE II. Rabies Postexposure Prophylaxis Schedule, United States, 1991

Vaccination Status	Treatment	Regimen*
Not previously vaccinated	Local wound cleansing HRIG	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. 20 IU/kg body weight. If anatomically feasible, up to one-half the dose should be infiltrated around the wound(s) and the rest should be administered IM in the gluteal area. HRIG should not be administered in the same syringe or into the same anatomical sites as vaccine. Because HRIG may partially suppress active production of antibody, no more than the recommended dose should be given.
	Vaccine	HDCV or RVA, 1.0 mL, IM (deltoid area [†]), one each on d 0, 3, 7, 14, and 28.
Previously vaccinated [‡]	Local wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water.
	HRIG	HRIG should not be administered.
	Vaccine	HDCV or RVA, 1.0 mL, IM (deltoid area [†]), one each on d 0 and 3.

* These regimens are applicable for all age groups, including children.

[†] The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.

[‡] Any person with a history of preexposure vaccination with HDCV or RVA; prior postexposure prophylaxis with HDCV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

vaccine was found to be safe and effective in protecting persons bitten by proven rabid animals and induced an excellent antibody response in all recipients.¹⁶ Studies conducted in the United States by CDC have shown that a regimen of one dose of HRIG and five doses of HDCV over a 28-day period was safe and induced an excellent antibody response in all recipients.¹⁵

Local Treatment of Wounds. Immediate and thorough washing of all bite wounds and scratches with soap and water is an important measure for preventing rabies. In studies of animals, simple local wound cleansing has been shown to reduce markedly the likelihood of rabies.^{50,51} Tetanus prophylaxis and measures to control bacterial infection should be given as indicated. The decision to suture large wounds should take into account cosmetic factors and the potential for bacterial infections.

Immunization. Two rabies vaccines are currently available in the United States; either is administered in conjunction with HRIG at the beginning of postexposure therapy. A regimen of five 1-mL doses of HDCV or RVA should be given intramuscularly. The first dose of the five-dose course should be given as soon as possible after exposure. Additional doses should be given on days 3, 7, 14,

and 28 after the first vaccination. For adults, the vaccine should always be administered IM in the deltoid area. For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for HDCV or RVA injections, since administration in this area results in lower neutralizing antibody titers.⁵²

Postexposure antirabies vaccination should always include administration of both passive antibody and vaccine, with the exception of persons who have previously received complete vaccination regimens (preexposure or postexposure) with a cell culture vaccine, or persons who have been vaccinated with other types of vaccines and have had documented rabies antibody titers. These persons should receive only vaccine (see Postexposure Therapy of Previously Vaccinated Persons). The combination of HRIG (local and systemic) and vaccine is recommended for both bite and nonbite exposures (see Postexposure Prophylaxis: Rationale for Treatment), regardless of the interval between exposure and initiation of treatment.

Because the antibody response after the recommended postexposure vaccination regimen with HDCV or RVA has been satisfactory, routine postvaccination serologic testing is not recommended. Serologic testing is only indicated in unusual instances, as when the patient is known to be immunosuppressed. The state health department may be contacted for recommendations on this matter.

HRIG is administered only once (ie, at the beginning of antirabies prophylaxis) to provide immediate antibodies until the patient responds to HDCV or RVA by actively producing antibodies. If HRIG was not given when vaccination was begun, it can be given through the seventh day after administration of the first dose of vaccine. Beyond the seventh day, HRIG is not indicated since an antibody response to cell culture vaccine is presumed to have occurred. The recommended dose of HRIG is 20 IU/kg. This formula is applicable for all age groups, including children. If anatomically feasible, up to one-half the dose of HRIG should be thoroughly infiltrated in the area around the wound and the rest should be administered intramuscularly in the gluteal area. *HRIG should never be administered in the same syringe or into the same anatomical site as vaccine.* Because HRIG may partially suppress active production of antibody, no more than the recommended dose should be given.⁵³

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Caruso and his doctors

ADRIAN W. ZORNIOTTI, MD

More than 30 years have elapsed since Prichard published his much quoted article, *The Death of Enrico Caruso*.¹ Prichard summed up what was known of Caruso's final illness, adding the results of his own inquiries. There has been no recent reappraisal of the medical aspects of Caruso's illness and although no major new evidence has surfaced, there is enough new, rediscovered, and unpublished material to make it appropriate to take this up again. The centennial of Caruso's birth (1973) was marked, in part, by several nonmedical articles about the man.^{2,3} In the past decades, three important biographies containing new material have appeared in English.⁴⁻⁶ Two of the most interesting accounts of Caruso's life have come from members of his immediate family.^{6,7}

A given of the opera world is that Enrico Caruso (1873-1921) was the quintessential singer, who succeeded in putting the grand into Grand Opera. Although other names can be advanced for discussion, Caruso's carries instant recognition and an aura that none other commands (Fig 1). His career, which was played out in the United States, coincided with an era when heroes like Theodore Roosevelt (1858-1919) and later Babe Ruth (1895-1948) were important to the fabric of American society. Having risen, Horatio Alger like, from very modest origins in Naples, Italy, he appealed to a public that, in time of minimal press agency, was very aware of his artistic and financial success, his generosity and benefactions, and his accessibility and *joie de vivre*. His death from peritonitis and sepsis was of operatic, even apocalyptic proportions.

Caruso worked hard and rarely disappointed an audience. The ability to achieve artistic success in his time was enhanced by a different pace of life than we have today. Then, a singer traveled to a city and settled down for the season. Singers today fly great distances from one appearance to another, perform with insufficient rehearsal time, and suffer from travel fatigue. From the time of his Metropolitan Opera debut in 1903 to December 24, 1920, when he sang that final *La Juive*, he gave 628 performances in that theater alone. In the final decade of his career, he made 40-50 appearances a year. His peak year at the Metropolitan was the 1907-1908 season when he made 70 appearances and grossed earnings of \$140,000.⁸ From 1903 to 1920, he cancelled scheduled performances 47 times, almost invariably

because of illness (personal communication, Martin Sokol, New York City, 1980). He made nearly 500 recordings, 248 of which were released largely by the Victor Talking Machine Company in the United States.

LAST AMERICAN TOUR

After his last performance of the 1919-1920 season on April 23, 1920, Caruso went on tour with the Metropolitan Opera to Atlanta for three performances. From there, he traveled to Havana where he gave 12 performances, the last of which was marred by a bomb explosion, apparently the work of someone who seems to have felt the ticket prices were too high, as indeed they were. He returned to New York City to a host of personal problems. The Hotel Knickerbocker on the corner of Broadway and 42nd Street, a short walk to the Opera House, was sold and converted into an office building, forcing him to move his home to the Hotel Vanderbilt at the corner of Park Avenue and 34th Street. Both buildings are still standing. The apartment he rented at the Vanderbilt was empty because it had belonged to Alfred Gwynne Vanderbilt who had died in the sinking of the *Lusitania* in 1915 (Fig 2). In addition, he rented a summer house in Easthampton, NY, and installed his family, which included his American wife Dorothy, their baby daughter Gloria, his son Enrico, Jr, by the Italian soprano Ada Giachetti, some of his in-laws who were guests, and an entourage of servants. At this time, Dorothy's jewelry was stolen during a burglary at the summer home, and he and his family were threatened with kidnapping and personal harm. These problems did not make it any easier for him to deal with recurrent headaches, spasmodic pains in his muscles of the neck, and hypertension from which he was known to have suffered for at least a decade. In a letter to his secretary, Bruno Zirato, dated August 3, 1920, he complained of vague generalized pains ("*dolori in genere*").⁹

Caruso enjoyed the pleasures of the table on days when he did not perform, and there is a great deal of documentation that he smoked heavily. His son stated that he was a chain smoker who inhaled deeply and even smoked surreptitiously while performing.^{6(p378)} Caruso told Ledner, his German manager, "If I cannot smoke, I cannot sing. Smoking is the only thing that calms my nerves." While performing in Germany, the absolute rule of no smoking on stage was bent to the extent that a fireman with a bucket of water was assigned to stand in

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FIGURE 1. Enrico Caruso: Inscribed photograph to his chiropractor, Francesco Sanichelli, who had offices at 2025 Broadway in New York City. This practitioner was quoted by the newspapers as saying that it was pressure from a misplaced vertebra on nerves in the spine, which caused the fatal abscess to form (Gift from Francis Robinson to the Author).

the wings while Caruso was performing.¹⁰ His favorites were Egyptian cigarettes from London that were called, with his permission, Selkowsky's Caruso Cigarettes (personal communications, Francis Robinson, New York City, 1960).

After his last Cuban performance on June 19, 1920, Caruso sang several concerts in the United States, including one at New Orleans on June 26th. After a vacation break in July and early August, the tour resumed, extending from Norfolk to Montreal (where he received \$10,000 on a gate of \$28,000) and into the western part of the United States. Throughout this extensive tour he was plagued by a persistent cold, which he described in an October 9th letter to Dorothy in prose that reflected his colorful English, "I think it was very bad to start the tour with my terrible cold. I feel it in my chester, and he will take a long time to go away."^{7(p220)} With the hardships of the tour behind him, life in New York City resumed in earnest. His most important task was to prepare for the upcoming season and opening night at the Metropolitan on November 15th, and there were rumors that he was not in the best of vocal form. Dorothy observed that he had returned looking "weary and worn" and that the "cold, instead of disappearing, had descended to his chest." Caruso's final illness had begun.



FIGURE 2. The Caruso apartment on the 18th floor of the Hotel Vanderbilt in New York City. The living room was converted into the operating room where Dr John Erdmann performed six operations for empyema. (Evening World, August 18, 1920).

ONSET OF THE FINAL ILLNESS

In 1920, Caruso's physician was Dr Philip Horowitz (a 1904 graduate of Columbia University College of Physicians and Surgeons) (Fig 3). Horowitz was a specialist in metabolic diseases at New York's Beth Israel Hospital.¹¹ When Dorothy's biography of Caruso appeared in 1945, her animus over what she saw as his incompetence was such that he could only be referred to as "Dr H." Horowitz initiated legal action against Dorothy and her publishers, Simon and Schuster, but his death ended the matter (personal communication, George Siegel, attorney with the firm of Lauterstein and Lauterstein, 1960) This matter is also mentioned in Mouchon's thesis.¹²

Dorothy's anger was based on the several instances when Horowitz had, in her opinion, misdiagnosed or trivialized Caruso's complaints so that the seriousness of the underlying disease was not recognized until other physicians were called in. Dorothy also characterized him as a quack:

I had seen him give Enrico ridiculous treatments for his headaches. These treatments consisted in laying him on a metal table, placing zinc plates on his stomach and sandbags on top of them. An electric current was then passed through the plates, and the spasmodic jerking of the bags was supposed to produce a super massage which would break up fat and cure the headaches. Next he was put in an electric cabinet and dehydrated. When it was all over he weighed several pounds less—which he regained, as soon as he got home, by drinking quarts of water. Since I couldn't prevent him from going to this doctor I didn't speak of my skepticism or protest when, one raw November day, he went again to Dr H to receive the same treatment for a cold in the chest that he had been given for a pain in the head.^{7(p232)}

Although Dorothy does not mention it, on December 3, 1920, Caruso was struck in the "back just below the left kidney" by falling scenery at the end of *Samson et Dalila*.^{6(p305)} That Caruso was actually struck is not confirmed in a long and detailed letter he wrote to Emilia Niola dated December 14th.



DR. PHILIP HOROWITZ

FIGURE 3. Dr Philip Horowitz (1882–1946), a graduate of the College of Physicians and Surgeons. Caruso's widow accused him of delaying the diagnosis of empyema (New York Academy of Medicine).

It is now exactly eleven days that I sang *Samson*. You should know that, when I sing this opera, something always happens to me, especially when I am blinded and in spite of the care I take in finishing the opera, there always happens a half a mishap when I throw down the columns, which even though are made of cardboard, still cause me such a contraction of the left flank that the tendons between the ribs become displaced, giving me terrible pain. To make this go away and before I go out to thank the public, I am obliged to throw myself to the ground and slide like a serpent until the said tendons return to their place. In the last performance of *Samson*, however, this incident did not repeat itself, and I was very happy.¹³

The day after the *Samson* performance, Caruso felt a chill while driving in Central Park and went directly to Dr Horowitz. Dorothy says he gave Caruso another electrical treatment. Key simply says he was sent home to bed.¹⁴ Caruso felt well enough to appear in *Pagliacci* on December 8th, at the midpoint of which, while singing a high note, he had severe left-sided pain, which was accompanied by malaise and momentary syncope. He was being examined by the physician on duty for the performance, Dr Emilio J. Sarlabous, when Horowitz intervened, saying that the matter was not serious and diagnosing intercostal neuralgia. Caruso finished the performance with his left chest strapped with adhesive tape.

During the months of November and December, Caruso's performances were uneven, possibly reflecting illness. Reviews varied and the Metropolitan management found it necessary to deny that he was ill. On December 11th, a very dramatic incident occurred when Caruso suffered hemoptysis during the first act of *Elisir*

d'Amore at the Brooklyn Academy of Music. In full view of the audience, he struggled to conclude the act, wiping blood from his lips. The performance was halted and after an examination, Horowitz concluded that a blood vessel had burst at the base of the tongue. A similar episode had occurred two years previously, according to Gatti-Casazza.¹⁵ That night, Caruso appears to have had an episode of dyspnea. Dorothy records that "he said, 'I must have air.' He left his bed and hurried to the open window. For a moment, he stared down at the street below, then began to climb over the sill. I put my arms around him and dragged him back."^{17(p238)}

Caruso sang on December 13th and 16th, but a scheduled performance of *Pagliacci* on December 22nd was cancelled. On December 21st, he again experienced severe pain and sleeplessness and felt the need to lean out of the window for air. Horowitz continued to insist that the problem was intercostal neuralgia and renewed the chest strapping. When Dorothy and his secretary, Zirato, begged Caruso to seek consultation with another doctor, he is said to have become furious.^{1(p384)} On Christmas Eve, he sang his last performance as Eleazar in *La Juive*. Although it was not apparent to the public, he was in pain and had to hang on to Florence Easton, who sang Rachel, to get through the performance.^{6(p308)} When it was over, he returned to the Vanderbilt, took a bath, and joined a small party at home.

CRITICAL MONTHS: JANUARY–MARCH 1921

Most biographers consider that Caruso became ill on Christmas Day, 1920, and, indeed, the critical phase of his illness did begin at that time. However, there is no doubt that the illness began before this. At 1 PM that day, Caruso suffered malaise and severe left-sided pain. He instinctively immersed himself in a hot tub. As the pain worsened he began to scream. His screams were audible on Park Avenue, 17 flights down. He was carried to a chaise longue where he was only able to sit on the edge, bent forward. Dorothy's account indicates that Horowitz could not be reached, possibly because it was Christmas. Thus, the Hotel Vanderbilt physician, Francis J. Murray, was summoned, and he administered hypodermic codeine (possibly morphine), which brought relief. A respected physician, Dr Evan M. Evans, was also called, and he examined Caruso, making a diagnosis of pleurisy. An account published several days later in the *New York Times* stated that Zirato, Caruso's personal secretary, called Horowitz who diagnosed pleurisy and then called Evans and Murray.¹⁶ Apparently, Dr Murray stayed close to Caruso's bedside throughout the night and kept the tenor sedated. On December 26th, a consultation was held that included Evans, Murray, Horowitz, and also Drs Samuel W. Lambert and Antonio Stella. Dr Lambert was a leading internist in the City and active in the New York Academy of Medicine; Dr Stella had his offices on East 16th Street and was very active in Italian-American affairs. His brother, Joseph, was a well-known painter. By this time, it was apparent that Caruso was suffering from bronchopneumonia. Prichard reported that a pneumococcus was isolated in Hans Zinsser's laboratory at the College of Physicians and Surgeons.^{1(p118)} In the light of subsequent events, this

finding is central to the infectious origin of Caruso's illness.

Except for statements that Caruso was better,¹⁷ there was no information on his progress. On December 29th, an ominous event occurred when Caruso became acutely dyspneic and cyanotic. Fortunately, Stella appeared at that moment and performed a thoracentesis with rapid relief of the symptoms. This signaled the need for a thoractomy to drain the now obvious empyema. A leading New York City surgeon, Dr John F. Erdmann, Chief of Surgery at the New York Postgraduate Hospital and Professor of Surgery at Columbia University College of Physicians and Surgeons, was called (Fig 4).

An operating room was set up in the salon of the apartment under the supervision of nurse Celeste Manion.¹⁸ At 6 PM Thursday, December 30th, a thoractomy was performed by Erdmann under local anesthesia. Caruso tells of his ordeal in a letter to his brother Giovanni: "I screamed for five days, seated on the edge of my couch day and night. Finally, what I remember is this: sounds of instruments being moved and jarred, and then as if they had placed the point of the knife in the spleen, and then great shouts of 'Urra.' What happened was that in making the incision to get to the ribs, the pus came out like an explosion striking the doctor, everything, the whole room."^{9(p135)} Erdmann said: "When his chest was opened, out poured the foulest pus I think I've ever seen and smelled."^{1(p118)} The operation was characterized as "only superficial," and Zirato took pains to tell reporters that there had been no resection of a rib.¹⁹ A drain had been inserted, and within 48 hours the patient was afebrile.

In a conversation with the urologist J. Sidney Ritter in 1969, I learned that he had assisted Erdmann during this procedure. He confirmed the accuracy of what was reported. There was no question of the diagnosis of

empyema. Ritter could not tell me the name of the anesthesiologist at the subsequent operations (personal communication, J. Sidney Ritter, New York City, 1969).

It was after this first operation that Dorothy had a confrontation with Horowitz. "When I saw him tripping toward me down the corridor . . . I said: 'I do not want you to come back here again. Please leave now and never come back.' . . . He didn't answer me, but started toward Enrico's door. I blocked the way. 'If you take one more step, I'll drop you out of that window.' He fled down the corridor, and I never saw him again."^{7(p245)} Sometime in the first week of February, Horowitz fell from a horse in Central Park and suffered a head injury.²⁰ He used this as an excuse to explain his withdrawal from the case and his having been dropped from the list of physicians issuing bulletins.^{6(p309)}

There is confusion with regard to the December 30th operation by Erdmann. The newspapers referred to this as the second operation, apparently having counted Stella's thoracentesis as the first procedure. The newspapers and the public were aware of only three operations, but Erdmann performed and billed for six.

On January 11th, the *New York Times* reported on an inside page that Caruso was convalescent. No further bulletins were issued until February 16th when he was again front page news. In the days prior to this, his fever returned and another operation (no. 2) which was not reported to the newspapers was performed on February 9th.^{6(p313)} Again, on February 12th, Erdmann reopened the chest, (no. 3) removing a four-inch segment of rib in order to probe more deeply. It seems reasonable to conclude that this procedure and the one of March 1st were performed under anesthesia. Over the next week, his condition remained poor, and on February 15th at about 10:30 PM he had what was characterized as a "sinking spell" and become comatose. This was attributed to a weakening of the heart but could just as well have been caused by sepsis. By February 18th, Murray was able to say that, "Mr. Caruso's temperature is lower, his pulse is better, and his mind much clearer than it has been."²¹

At this time, two events should be noted. During Caruso's convalescence, x-ray equipment must have been brought to the Vanderbilt to do a radiograph of the chest. Even today, such equipment is not considered readily portable. The findings was that his left lung "had contracted." The other was the appearance of paresthesias and weakness of the right hand with atrophy of the interosseus muscles. As Prichard pointed out, the probable cause of this was right brachial plexus palsy from improper placement in a flank position for surgery to the left chest^{1(p118)} or from lying on his right side while comatose. Thereafter, Caruso only appeared in public wearing a glove on his right hand.

Further incision and drainage of an abscess was performed on March 1st (no. 4) possible the one for an abscess described by Dorothy as being "between the hip and the ribs, due to poisonous seepage from the pleura."^{7(p252)} Two lesser procedures were performed on March 15th and 25th. It was probably between these two dates that Caruso received the first of two, possibly direct (there was no blood banking then) blood transfu-



FIGURE 4. Dr John F. Erdmann (1864–1954) was one of New York City's leading surgeons (New York Academy of Medicine).

sions administered by Dr Lester J. Unger and given by Everett Wilkinson of Meriden, Connecticut. In the 1920s, blood donors were referred to as "givers" a term that survives today when one "gives blood." The decision to transfuse was clearly the right one, and convalescence now accelerated, reaching a point where his doctors, in consultation, approved his departure for Italy in May. Following this, Caruso had a meeting with Edward Ziegler, Assistant General Manager of the Metropolitan, to discuss his plans for the fall. It was Caruso's intention, Ziegler wrote in a memo to Gatticasazza, to return one month before the season opened to resume his "duties."²²

Caruso, who weighed 225 pounds, had lost over fifty pounds during his illness, but he remained afebrile and was regaining weight and strength. He was left with scars below the left scapula, and there remained a small opening, which was covered by a small dressing fixed to the skin with adhesive tape.^{6(p321)} Preparations for sailing on an Italian liner, the *S.S. Presidente Wilson*, on May 28th included paying his doctor bills in addition to all the other expenses connected with his illness, which were considerable. No information has been found concerning fees owed to Dr Evans, the unidentified radiologist, or to Dr Unger. He paid the following practitioners based on receipted bills (author's collection) and by examination of stubs of checks drawn on the Fifth Avenue Bank (Robinson Collection—Heard Library, Vanderbilt University): \$17,500 to Erdmann for six operations, \$15,000 to Stella, \$17,500 to Murray, and \$3,300 to Lambert. (Fig 5-7)

According to Dorothy, Horowitz did not submit a bill, and this did not escape Caruso's notice. He therefore

Telephone 976 Circle Office Hours 11:30 A.M. to 1:00 P.M.
100 East 35th Street

New York May 28 1921

Mr Enrico Caruso, Vanderbilt Hotel

To Dr. John F. Erdmann, D.O.

For professional services Operations - 6 -
Treatment

From Dec 30 - 1920
to May 26 - 1921
Inclusive \$17,500⁰⁰

Paid May 27 - 1921

With thanks
John F. Erdmann

Bon Voyage H.E.

FIGURE 5. Erdmann's bill evidently included all consultations with the other doctors who cared for Caruso and possibly fees for surgical assistants (Gift from Francis Robinson to the Author).

214 EAST 16TH STREET
NEW YORK 1921
May 26th

Comm, Enrico Caruso
Vanderbilt Hotel

TO ANTONIO STELLA, M. D.

FOR PROFESSIONAL SERVICES

From December 26th 20 to January 19th 21	\$ 5,000.00
From January 20th to February 3rd	750.00
From February 4th to March 19th	9000.00
From March 20th to May 26th	1100.00
Reduced 1/5 \$15,000	\$ 15,850.00

RECEIVED PAYMENT

Antonio Stella

STATEMENTS RENDERED MONTHLY
AN ITEMIZED ACCOUNT MAY BE HAD IF DESIRED

Con saluti ringraziamenti.

FIGURE 6. Antonio Stella's bill. Stella saw Caruso, several times a day, and at a critical moment he aspirated Caruso's empyema, relieving severe dyspnea and cyanosis (Gift from Bruno Zirato to the Author).

sent Horowitz's wife a gift of jewelry of a value equivalent to \$15,000, which Dorothy said was "the smallest bill from any of the doctors."^{7(p255)} However, the smallest bill of which there is a record was that of Lambert for \$3,300. Caruso was also annoyed by Stella's bill (ultimately reduced to \$15,000) on learning that Stella had said that the demands of caring for Caruso had affected his other earnings (personal communication, Francis Sisca, New York City, 1980). Although these bills were admittedly high, there is no question that these men, particularly Murray, devoted enormous amounts of time to Caruso. Lambert, for example, saw Caruso or had discussions with the other physicians 66 times, and Stella, who had saved his life by emergency thoracentesis, saw him daily and sometimes oftener for nearly six months.

On the day before sailing, Caruso paid a visit to the radiologist who had performed chest examination. He

454 100 EAST 35TH STREET NEW YORK May 24 1921

Sign Enrico Caruso
Hotel Vanderbilt

TO SAMUEL W. LAMBERT, M. D., D.O.

TO PROFESSIONAL SERVICES

66 Consultations, incl. 64. Exam, History, Urethra, Mucosa, + Stella \$3300.

RECEIVED PAYMENT

Sam W Lambert

FIGURE 7. Samuel W. Lambert's bill (Gift from Bruno Zirato to the Author).

was not in, but his assistant told Caruso that his rib had already grown back half an inch. "There was no way to stop what followed. The young doctor brought Enrico the x-ray plates and showed him where four inches of his rib had been removed."^{7(p258)} The carefully guarded secret was out. Caruso, along with others, believed that such a loss would permanently impair a singer's ability to produce the column of air needed to sing.

SORRENTO, ITALY

On May 28th, the Caruso family sailed for Naples as planned. (Fig 8) At the height of his illness, Caruso had expressed the wish to die in Italy, and when it became evident that he was recovering, wished to convalesce in the Italian sunshine. It is doubtful that anyone thought that he was soon to die a short distance from his birthplace in the city with which he had a love-hate relationship.

The ship carrying Caruso, his wife Dorothy, and small daughter Gloria, docked on June 10th. For 10 days, he was with his family, including his 23-year-old son Rodolfo by the Italian soprano Ada Giachetti, and old friends. Caruso enjoyed Naples but steadfastly refused to sing there after having been affronted in 1905 by what he interpreted as a hostile reception by his fellow Neapolitans to his performance in *L'Elisir d'Amore*. This was instigated by an audience clique, which acted as the artistic arbiter of the San Carlo Opera House, giving rise to a quote that has several variations: "I will only go to Naples to have the pleasure of seeing my mother and to eat vermicelli with clams." He then crossed the Bay of Naples to Sorrento, to stay at the Hotel Vittoria, perched on a cliff overlooking the bay. The accommodations were luxurious, and meals were served from the hotel kitchen as was his habit everywhere he went.

Rodolfo wrote that he was alarmed by his father's emaciated appearance and the ashen color of his face at the time of his debarkation.^{6(p320)} However now, in

Sorrento, Caruso gained weight, felt better, and his color improved. In a letter to Zirato who stayed behind in New York City, he said that his health was better, that he was walking one kilometer every day, and that the wounds were all closed except for the "lower one on which there has formed a small opening with proud flesh (*uno zippolino di carne cresciuta*) which is not able to find the way to go away . . . My hand has become thinner and the internal sensation is always the same. I have begun mud baths and massages for which there is much hope."^{12(p624)} Dorothy applied iodine to the open area and dressed it daily. Caruso sat on the terrace and drank coffee while he immersed his hand and arm in hot medicinal mud sent over daily, by boat, from Agnano Terme.

Caruso sunbathed and swam in the bay, even though his incision was not fully healed. As he felt better, he broadened his activities to include seeing the many visitors who came to Sorrento, outing to Capri, and to the church of Our Lady of Pompeii, leaving 10,000 lire (about \$2,000), to give thanks for his recovery. Dorothy objected to this socializing because she had misgivings about interrupting a quiet convalescence and was mindful of the warnings of the New York doctors not to place a strain on his weakened heart (Fig 9). It was around this time that Caruso discovered that his voice was intact and still beautiful, and the loss of a section of rib had not meant the end of his career. Letters and telegrams to the United States were upbeat, and Caruso and his entourage were optimistic about his convalescence and continued career.

Sometime after July 15th, Dr Raffaele Niola, the elderly family physician, paid a visit. Dorothy returned from the beach with Gloria to find Caruso lying down: "An old, old man was bending over him. He held a probe in his hand, and I saw that that hand was dirty." "This is the doctor who took care of my dear mother," Enrico said. "What is he doing with that probe?" I asked. "I just show him my scars . . ." "He should wash his hands before touching you." "I know, but I do not like to hurt his feelings, my Doro." Before she could stop him, the doctor "lifted the little crust—and pushed the



FIGURE 8. Departure for Naples, S.S. *Presidente Wilson*, May 1921. The convalescent Caruso is seen with his wife Dorothy Park Benjamin Caruso and young daughter Gloria (b. 1919). Caruso is wearing a glove on his right hand to conceal hand muscle atrophy, probably from brachial plexus palsy at the time of operation (Robinson Collection, Vanderbilt University).



FIGURE 9. Group photograph taken July 27, 1921; at the Hotel Vittoria in Sorrento. Dorothy, Gloria, and Caruso are seated at the table. Standing behind the tenor is his son Rodolfo by the Italian soprano, Ada Giachetti. The standing women is Gloria's Swedish nurse. The others are Errico Scognamiglio and his family (Robinson Collection, Vanderbilt University).

unsterilized probe into the old incision." The next morning, Dorothy reports, Caruso had a fever of 101°F but refused to see a doctor. She used Caruso's friendship and respect for Giuseppe de Luca, the well-known baritone, to persuade him to be seen by a physician.^{7(p268)}

THE FEVER RETURNS—MEDICAL CONSULTATIONS

While in Sorrento, Caruso was seen by several physicians. One, whose consultation is not mentioned by any biographers, was Dr Giuseppe Moscati (1880–1927) (Fig 10). Moscati's student, Polichetti, in a 1956 memoir of his mentor, wrote that Moscati told his students: "At the end of July, I examined Enrico Caruso for the first time in Sorrento at the Hotel Tramontano [sic]. He had been operated in America for purulent pleurisy without being cured." Moscati "made the diagnosis of subphrenic abscess, heretofore undiagnosed, by the extraction of pus by means of a puncture of the sub-diaphragmatic space."²³ Polichetti went on to say that Moscati's modest charge was 2,000 lire (about \$400) for the consultation, diagnostic puncture, travel to Sorrento, and a subsequent visit in Naples.

Polichetti's report is uncorroborated by either of the two family members, Dorothy and Rodolfo, who were in Sorrento. Rodolfo's memoir, published by his brother, relates that, when he realized that the medical situation was beyond his capabilities, Dr Niola "called in several famous professors from Naples for a consultation."^{6(p326)} Shortly after Caruso's death, Moscati gave an interview, which was quoted in *Il Progresso Italo-Americano* of New

York²⁴, and he did not mention seeing Caruso in Sorrento.

Moscatti made an important point regarding a side effect of long-standing infections, one which no other author has suggested, "Enrico Caruso died of a subphrenic abscess complicated by a purulent pleurisy, already operated on in America, of generalized sepsis and from the inevitable consequences of amyloid degeneration of the liver and kidneys, after nine months of suppuration and useless treatment."^{22(p486)}

The visit on July 28th by the highly respected Bastianelli brothers, Raffaele, (b. 1863) a surgeon, and Giuseppe, an internist and malariologist follower of Marchiafava, has been extensively documented. The two flew to Naples from Rome, as Raffaele was one of the first to earn a private pilot's license in Italy.²⁵ Both men spoke English and had extensive medical contacts in Great Britain and the United States. In addition, they were both married to Americans from Pennsylvania (personal communication, Robert Prichard, Winston-Salem, 1990) so that their visit came as a relief to Dorothy who, surrounded by Italians, was without the usual support from her sick husband. Dorothy also was glad to be able to "tell them the complete history of Enrico's illness and show them the New York laboratory reports, as well as the daily record kept by Zirato."^{7(p268)} The examination took 20 minutes, and according to Dorothy they said that Caruso had a subrenal abscess probably involving the left kidney. They proposed that Caruso come to their clinic (private hospital) in Rome to have a nephrectomy but said that there was no hurry.^{7(p269)} In Dorothy's 1928 version of the consultation the Bastianellis were quoted as saying: "There was undoubtedly an abscess close to the kidney."²⁶ In a letter dated July 29th to his friend and editor of the Italian newspaper *La Follia di New York*, Marziale Sisca, Caruso wrote that he was to be in Rome on August 3rd to have x-rays (*radioscopia*).²⁷ Rodolfo's version has it that the Bastianellis said: "He must have an operation as soon as possible."^{6(p328)}

Prichard wrote (1959) that the Bastianellis did not agree with what Dorothy had published concerning their diagnosis and proposed treatment but chose to remain silent on the matter.^{1(p119)} When Prichard sent Raffaele Bastianelli a reprint of his article, he received the following reply: His brother having died, Raffaele decided to break the silence and correct the diagnosis on the basis of the two brothers' notes made on July 28, 1921. He said that it was not a subrenal but a subphrenic abscess and that Caruso was to have x-rays and surgery appropriate to the findings. Raffaele also wrote: "I don't know why he delayed to come to Rome." This letter to Prichard, dated October 5, 1959, was published, in facsimile, by Mouchon.²⁸ The *New York Times*, just after Caruso's death, quoted the Bastianellis as saying, "After careful examination, we both agreed that the present and past sufferings of the great tenor was derived [sic] from a subrenal abscess."²⁹ It is possible that Dorothy, in preparing her manuscript, followed the newspaper accounts, but it does not seem likely that the brothers were quoted incorrectly by the news services.



FIGURE 10. Giuseppe Moscati (1880–1927). May have been the first to diagnose Caruso's fatal subphrenic abscess (Author's collection).

FINAL DAYS

After the departure of the Bastianelli brothers, there was hesitation. Just how urgent the matter appeared to those involved is not clear, and July 29th and 30th slipped by, while fever, sweating, and disorientation increased. Finally, Caruso's deteriorating condition and Dorothy's insistence on waiting no longer made departure for Rome imperative. Caruso's younger brother, Giovanni, came from Naples, his task being to make arrangements for the trip and to help convince Caruso to begin the journey to Rome. Giovanni arrived early on Sunday, July 31st, and the party took the noon ferry to Naples. The plan appears to have provided for an overnight stay at the Hotel de Vesuve. A train was chartered to take the party to Rome the next day, August 1st. The ferry crossing was uneventful, and Caruso chatted with the other passengers.^{6(p330)} On debarkation in Naples, the party went directly to the hotel, occupying suite 45.^{12(p632)}

DOROTHY'S VERSION

What transpired can probably be best summed up by what Dorothy ruefully told Francis Robinson some 30 years afterward: "Never get sick in Naples in August" (personal communications, Francis Robinson, New York City, 1960s). On the night of July 31st, Caruso managed to sleep in spite of a fever of 104°F, was alert, and sat up in bed the next morning. Without warning, he began to scream, as he had in New York, and broke out into a profuse diaphoresis. It was four hours before a doctor could be found and morphine given. Eventually, six doctors responded. "They proposed to remove the left kidney but dared not give complete anesthesia because his heart would not stand the strain . . . If they didn't operate, he would die before morning. It was I who must make the decision." Dorothy insisted: "Before you start the kidney operation, I ask first to open the lower incision in his side, under the scar. Go in four inches with your fingers and feel for an abscess the size of a walnut. Break it and insert a drain—I will take the responsibility. After an hour they called me back in and announced that it was useless to operate at all. I pleaded with them with all my strength to probe for the abscess, but they refused. 'At least give him a blood transfusion,' I begged. This they also refused."^{7(p270)}

MOUCHON'S VERSION

Dr Jean Pierre Mouchon became interested in Caruso on hearing one of his recordings in a music shop in France. His detailed thesis in the Library of the Sorbonne is a lode of information.¹² The first doctors to arrive and see Caruso in the hotel room were Professors Piscitelli, De Martini, and Pellegrini. They concluded that Caruso's condition was very grave, finding abdominal dullness in the left diaphragmatic and renal regions extending to the right above the liver. On palpation, the area was very painful, and they could discern what they believed to be a purulent collection. In the abdomen, there was pain along the colon with rebound. The patient had a filiform pulse and fatigue of the heart. An operation was judged useless.

Dr Niola, the *medico curante* (treating physician), administered camphor in oil and oxygen. At 10 PM, a second consultation took place with Professors Raffaele Chiarolanza, Gaetano Sorge, Gennaro Sodo, and Moscatti. Chiarolanza (b. 1881) made the decision to wait until 8 AM the next morning, August 2nd, at which time it was decided that the patient could not survive an operation. By 9 AM Caruso's condition had worsened perceptibly, and one half hour later he was dead.

CHIAROLANZA'S VERSION

This version is from an unidentified Italian newspaper clipping, probably published shortly after Caruso's death. The nearly complete translated version appears in Enrico Caruso, Jr's biography.^{6(p394-7)} A copy of the article, signed by Chiarolanza, was provided by Professor Farkas.

When Moscatti, Sorge, Sodo, Niola, and Chiarolanza gathered, the extreme gravity of the disease was obvious. Caruso had signs of septic peritonitis and septicemia. There was constant restlessness; distressed (anxious) respiration; rapid pulse (140/minute); tenderness throughout the entire abdomen; intestinal obstruction also to gas; inability to tolerate any fluid, including water, in spite of a burning thirst; profuse sweats; suppression of urine, confirmed by catheterization; fallen facial contours with sunken eyes surrounded by livid rings; the picture of a generalized infectious process, which was progressing precipitately.

The doctors concluded that, although surgery was the only means by which some help could be offered to the patient, the moment of surgical opportunity to attack the original seat of the disease was already gone. It was decided to attempt to relieve the patient's condition with appropriate treatment and postpone any surgical procedure until 8 AM. By 7 AM of the next day, Caruso's fate was decided, and in a few hours he was dead.

Chiarolanza went on to say that the disease began as a subdiaphragmatic abscess which, from the beginning, affected the pleura as is "natural and usual." In his opinion: "The pleural signs of the disease predominated the clinical picture, and this explains why the American doctors, who had diagnosed the first sufferings of the patient as rheumatic, fixed their attention on the pleura alone. The American doctors did not consider the possibility of a subphrenic abscess, otherwise they would have discovered it." Chiarolanza also opined that the failure of the various operations should have alerted the American surgeons that they were on the wrong track. He concluded that it would not have taken much to do a "properly" done x-ray to resolve all doubts, if clinical observation and common sense were not enough. "Unfortunately, the failure to see the reality in America, was followed by an incomprehensible, let us say, fatalism in Naples. If a timely diagnosis had been made in Naples, Caruso would have been saved." The abscess itself was not the cause of death but an intricate series of complications that certainly would have been avoided had there not been loss of time and that Caruso was allowed to neglect his health. Had Caruso been operated ten days previously he would have been cured.

humor. Nor was *Don Marzio* spared. Less than a week after the tenor's death, Professor Cardarelli, who was Naples' leading teacher and clinician and who had not seen Caruso, was depicted in a cartoon in the humorous weekly *6 & 22*, holding the *Don Marzio* headline in his hand while chiding two colleagues for their part in the medical brouhaha that ensued.³² (Fig 12)

Caruso's remains were eventually transferred to a mausoleum. There had been doubt that a satisfactory embalming could be achieved, owing to the presence of sepsis.^{6(p336)} Those responsible had good reason to be proud of their handiwork for, as is the case with venerated saints, the coffin lid was made of heavy glass so that the body dressed in morning clothes and decorations could be viewed by the curious. It took years of battling with the municipal and ecclesiastical bureaucracies by his appalled American widow to get the coffin permanently closed.^{6(p421-2.)}

Acknowledgments. The author wishes to remember the late Francis Robinson whose enthusiasm for Caruso was legendary. Working on the translation of a Caruso letter for Robinson's book, in which Caruso described his operation to his brother, fired my interest in the tenor's medical problems and the doctors who treated him. I want to thank the late Bruno Zirato for providing the doctor's bills and much useful information about Caruso. Thanks too are due to Professor Andrew Farkas and Doctor Robert W. Prichard for making material available from their files and much useful information. I would like to recall a urological colleague, the late J. Sidney Ritter who assisted at one of the operations. The Sisca brothers, Francis and Michael, for several informative conversations over dinner at their home. Thanks are also extended to Robert Tuggle, Howard Greenfeld, and Martin Sokol for sharing their scholarly knowledge. Thanks are also due to Marice Wolfe, Mary Ann Jensen, Dr Silvana Musella, and Edwin Quist for help in searching collections under their curatorship.

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Association of asbestos exposure, retroperitoneal fibrosis, and acute renal failure

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We report the temporal association between the development of retroperitoneal fibrosis and the progression of diffuse pleural thickening in a patient previously exposed to asbestos. Acute renal failure caused by ureteral obstruction by a retroperitoneal fibrotic process occurred within six weeks of a pulmonary evaluation for diffuse pleural fibrosis. The patient had no known risk factors for retroperitoneal fibrosis.

CASE HISTORY

A 72-year-old male presented with complaints of increasing dyspnea on exertion and vague discomfort in the chest for approximately six months prior to admission. There was no history of cough, fever, hemoptysis, pleuritic chest pain, or urinary symptoms. The occupational history was remarkable for exposure to asbestos between 1941 and 1945, when he worked as a machinist in a shipyard. He may have experienced additional asbestos exposure when he worked as a pipefitter for several months in 1970. The patient had also worked for 32 years as a taxi driver in New York City. He had never smoked. The medical history was noteworthy for two myocardial infarctions and coronary artery bypass surgery in 1984. The patient had otherwise been healthy and specifically denied any history of lung, pleural, or renal disease. He had been taking the following medications since his coronary artery bypass surgery four years previously: digoxin, 0.25 mg once daily; nitroglycerin controlled-release capsules, 2.5 mg twice daily; dipy-

ridamole, 75 mg three times per day; and aspirin, 80 mg once daily.

The physical examination was unremarkable except for decreased breath sounds at the left lung base. The prostate was mildly enlarged, and the stool was negative for occult blood. Chest roentgenograms showed bilateral pleural thickening (Fig 1), which had increased on the left when compared with a chest roentgenogram done four years previously (Fig 2). Computed tomography of the thorax (Fig 3) demonstrated mild pleural thickening in the right upper thorax, severe pleural thickening (1.0–1.5 cm thickness) on the left inferior and posterior thorax, and a 2-cm nodular density contiguous with the left posterior pleura. Calcification of pleura or increased interstitial lung markings were not identified. There was a restrictive pattern on pulmonary function tests (forced vital capacity, 2.29 L, 51% predicted; total lung capacity, 3.90 L, 55% predicted) and a reduced single breath diffusion capacity (DL_{CO} 16.63 mL/mm/min, 53% predicted; DL_{CO}/V_A 4.84 mL/mm/min/L, 106% predicted). The blood chemistry profile at this time was normal except for a glucose level of 155 mg/dL. The serum creatinine was 1.3 mg/dL. The hematocrit was 41.3%, and the white blood cell count was 10,800/mm³ with a normal differential count.

An open pleural biopsy, performed to rule out the possibility of a pleural malignancy, was interpreted as chronic active and organizing pleuritis and dense fibrosis. This pattern of organization was consistent

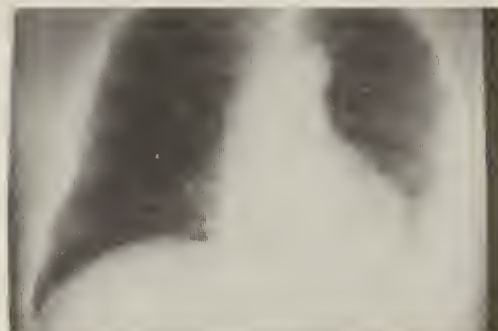


FIGURE 2. Chest roentgenogram obtained in April 1988 demonstrating an increased left pleural thickening when compared with study from 1984.

with a pleural plaque or with diffuse pleural fibrosis. The patient was discharged home with a diagnosis of asbestos-related diffuse pleural fibrosis. He was continued on his preadmission medications and advised to return four months for follow-up evaluation.

Six weeks after the pulmonary evaluation, the patient returned with a one-month history of progressive weakness, malaise, anorexia, and a five-pound weight loss. The physical examination and chest roentgenograms were unchanged from six weeks previously. The chemistry profile showed a blood urea nitrogen (BUN) of 63 mg/dL; creatinine, 4.5/dL; potassium, 5.3



FIGURE 1. Chest roentgenogram obtained in October 1984 demonstrating mild bilateral pleural thickening.

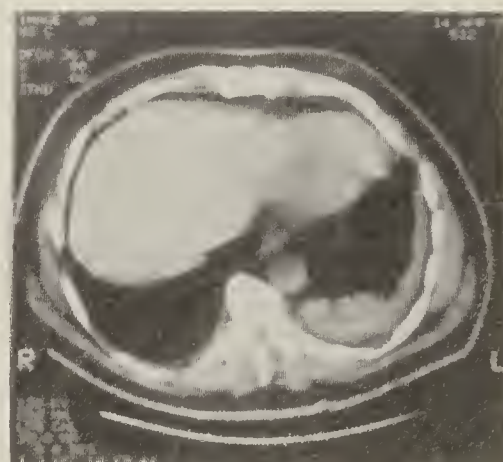


FIGURE 3. Computed tomogram of the chest obtained in April 1988 demonstrating mild right pleural thickening and more severe left posterolateral pleural thickening. A 2-cm nodular density is contiguous with the left posterior pleura.

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mmol/L; and phosphate, 6.2 mg/dL. The hematocrit was 32.7%, and the white blood cell count was 11,400/mm.³ The urine specific gravity was 1.006, and the pH was 5. There were no cells, casts, or protein found in the urine.

An abdominal ultrasound demonstrated bilateral hydronephrosis. A magnetic resonance imaging (MRI) scan confirmed the bilateral hydronephrosis. Bilateral hydroureters were also seen on MRI scan to the level of the proximal iliac arteries, where fibrosis was noted surrounding the distal abdominal aorta and proximal iliac arteries. There was no evidence of an aortic aneurysm. A renal hippuran scan revealed negligible to absent right-sided renal function, with a severely dysfunctional left kidney. Cystoscopy and retrograde urography revealed mild prostatic hypertrophy, complete obstruction of the right ureter at the level of the first sacral vertebral body and partial obstruction of the left ureter at the level of the fifth lumbar vertebral body.

The prostate was biopsied and found to have adenomatous and fibromuscular hyperplasia. A left ureteral stent was placed, with gradual improvement in renal function during the subsequent week. The patient then underwent repeat cystoscopy and exploratory laparotomy. Intraoperative findings included retroperitoneal and peri-iliac fibrosis with encasement of the right and left ureters in the fibrotic process. Retroperitoneal fibrosis and periureteral adhesions were lysed, a segment of the right ureter was resected, and the ureter was reanastomosed. Bilateral ureteral stents were placed.

Pathological examination of the tissues revealed fibrocollagen tissue with chronic inflammation and lymphoid aggregate. The resected ureteral segment was found to have periureteral fibrosis with segmental fibrocollagen replacement of ureteral muscle coat and subepithelium. The findings were consistent with retroperitoneal fibromatosis with invasion of the right ureter.

The postoperative course was complicated by cardiac arrhythmias that were presumably provoked by the significant electrolyte shifts in the perioperative period. At the time of hospital discharge, the serum creatinine was 1.7 mg/dL, and the BUN was 18 mg/dL.

The patient has been observed in the outpatient department for 36 months since his hospital discharge without further progression of his symptoms. The serum creatinine remains unchanged at 1.8 mg/dL. The chest roentgenogram, complete blood count, and chemistry profile remain unchanged. Pulmonary function tests are unchanged except for some decrease in forced expiratory flow rate (FEF₂₅₋₇₅), which may indicate an obstructive component localized in smaller airways.

DISCUSSION

Pleural plaques are discrete collections of collagenous connective tissue

on the inner surface of the rib cage and diaphragm. The relationship between pleural plaques and asbestos exposure has been confirmed by population studies, and the prevalence of these pleural plaques on chest roentgenograms has been shown to be related to the duration and severity of asbestos exposure.^{1,2} Diffuse bilateral pleural thickening, as was seen in the patient described here, has recently been recognized with increased frequency and has also been strongly associated with asbestos exposure. In contrast to pleural plaques, diffuse pleural thickening is a smooth, noninterrupted pleural density extending over at least one fourth of the chest wall and often involving costophrenic angle obliteration.^{3,4} This diffuse pleural thickening can result in severe restriction of lung function and can even result in clinical respiratory failure.^{5,6} The histologic pattern can closely resemble that of a pleural plaque.⁷ In this report, we describe an asbestos worker who had retroperitoneal fibrosis and obstructive renal failure in association with progressive asbestos-related diffuse pleural disease.

This patient's primary respiratory symptom, dyspnea on exertion, developed over the six months prior to development of retroperitoneal fibrosis. A comparison with chest roentgenograms done three years previously indicated an increase in thickening of the left posterior pleural and the suggestion of a left posterior pleural-based mass lesion. The biopsy was consistent with diffuse pleural fibrosis. The roentgenographic increase in pleural thickening was associated with clinical dyspnea and was significant enough to impair lung function, as measured by reductions in lung volumes and single breath diffusion capacity. The absence of interstitial lung disease on the chest roentgenogram or computed tomography of the thorax suggests that the restrictive lung defect is best explained by diffuse pleural disease and entrapment of the underlying lung. Furthermore, the diffusing capacity was found to be within the normal range when corrected for the decrease in lung volume. Wright and colleagues⁵ have described six cases of a restrictive lung function pattern in patients with asbestos pleurisy, with no evidence of interstitial lung disease.

More than two thirds of patients with retroperitoneal fibrosis have no identified etiologic factors; their condi-

tion is referred to as idiopathic retroperitoneal fibrosis.^{8,9} The remaining cases are thought to be caused by malignancy, inflammation around aneurysms of the abdominal aorta, retroperitoneal hematomas, infection, radiation, or are associated with various drugs. Drug-induced retroperitoneal fibrosis has been associated most clearly with methysergide, but an association has also been reported with other ergot derivatives and with various antihypertensive agents, such as beta blockers, alpha-methyldopa, hydralazine, and reserpine.⁹ There have been several case reports of retroperitoneal fibrosis in patients with analgesic abuse. The reported patients ingested large quantities of various analgesics, including aspirin, over many years.^{10,11} The patient presented here ingested a single 80-mg aspirin tablet daily for four years as part of his treatment for arteriosclerotic heart disease. Retroperitoneal fibrosis is not likely to be related to this amount of aspirin ingestion. In the reports of analgesic abuse associated with retroperitoneal fibrosis, patients ingested 20 to 80 times as much aspirin daily, usually in combination with other analgesics such as phenacetin, codeine, or propoxyphene.^{10,11}

It has also been suggested that retroperitoneal fibrosis may be a reaction to an antigen in aortic atheroma. Retroperitoneal fibrosis often occurs in patients with abdominal aortic aneurysms, and the fibrosis may encase areas of the aorta where severe atherosclerotic plaques may actually be breaching the media. Ceroid is an insoluble lipid found in the base of necrotic atheromatous plaques. When the aortic media is thinned, ceroid from the atheromatous plaque may leak into periaortic tissues and induce an immune response.¹² The patient described here did have significant coronary heart disease, but he did not have any evidence of aortic aneurysm in association with his retroperitoneal fibrosis. It would be difficult to explain how an immune response to ceroid leaking from arteriosclerotic plaques could explain the significant pleural fibrosis. Corticosteroid therapy has been used to treat the inflammatory component of retroperitoneal fibrosis.^{8,9} In the patient described here, it was decided that the potential risk associated with corticosteroids were excessive, and these medications were not prescribed. Corticosteroids have not been shown to be an effective

therapy for pulmonary asbestosis or pleural fibrosis.

The development of retroperitoneal fibrosis in this patient occurred in temporal association with the increase in pleural fibrosis. There is reason to infer that the etiology of both the pleural and retroperitoneal fibroses are the same in this case. Although inhalation of asbestos fibers is usually associated with pulmonary or pleural disease, Auerbach et al¹³ identified asbestos bodies in most major organs, including retroperitoneal organs such as the kidney and adrenal glands, in autopsy material obtained from asbestos workers.¹³ Peritoneal mesotheliomas have been reported to be associated with exposure to asbestos. In some series, peritoneal mesotheliomas are actually more common than pleural mesothelioma.^{14,15} Asbestos fibers may gain access to the retroperitoneal space via the gastrointestinal tract or via lymphatic drainage from the lung. Mesothelioma was not considered in this case because pleural and retroperitoneal biopsies revealed fibrosis without evidence of malignancy, and the 36 months of clinical follow-up without progression of symptoms is not consistent with the clinical course of mesothelioma.

Retroperitoneal fibrosis developed in this patient in the absence of any of

the usual predisposing factors. The retroperitoneal fibrotic process was severe, entrapping both ureters and resulting in obstructive renal failure. The pleural fibrotic process was also severe enough to cause a restrictive ventilatory defect. In some individuals, asbestos-related fibrosis has been reported to be so severe as to result in mediastinal fibrosis with occlusion of spinal and intercostal arteries and resultant paraplegia.¹⁶ It is possible that this patient's retroperitoneal fibrosis was part of the same progressive fibrotic process that involved his pleura and was associated with his prior asbestos exposure. Therefore, it is important to consider prior asbestos exposure in the history and evaluation of patients with retroperitoneal fibrosis.

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Infected mesenteric lymphangioma

RICHARD J. RICCA, MD

CASE REPORT

Mesenteric lymphangioma is a rare congenital cyst of the mesentery. It may present as a painless abdominal mass or as abdominal pain due to rupture and hemorrhage, which may be spontaneous or follow trauma. We present a case of a septic patient with an acute abdomen and a large abscessed abdominal mass treated by enucleation of the infected cyst and resection of the adherent small intestine.

A 27-year-old woman presented with a two-week history of diffuse abdominal pain and fever. She complained of nausea but no vomiting. She had been seen in the emergency room one week prior to admission and was thought to have gastroenteritis. The nausea, pain, and fever persisted, and she returned to the emergency room. At that time, she appeared acutely ill, volume-depleted, and febrile, with a temperature of 103°F. The abdomen was diffusely distended and no bowel sounds were heard. There was diffuse lower abdominal tenderness with rigid guarding and rebound. The pelvic examination revealed a thick yellowish green discharge consistent with *Trichomonas* infection. Anterior to

the uterus and extending out of the pelvis was a large, extremely tender, cystic mass, which seemed to occupy the midline. There were no skin abrasions.

A CBC, SMA 7, and amylase levels were normal. Urinalysis showed *Trichomonas*. Abdominal radiographs showed pattern suggestive of ileus. The sonogram demonstrated a large cystic, pelvic mass, which was septated with some internal debris. The mass measured 14 cm in the craniocaudal dimension, 9.4 cm in the anteroposterior dimension, and 11.7 cm in the transverse dimension (Fig 1).

The presumptive diagnosis was an infarcted, twisted adnexal mass, and the patient was brought to the operating room and underwent exploration through a Pfannenstiel's incision. An infected mesenteric

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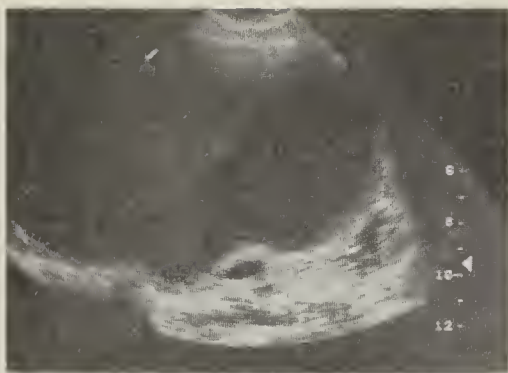


FIGURE 1. Sonogram showing large cystic pelvic mass with internal debris.

mass, the size of a football, arising from the root of the small bowel mesentery, and with small bowel intimately draped over it, was identified. A trocar was placed into the mass, and one liter of purulent fluid was drained. The abscess was completely adherent to the mesenteric border of the mid-small bowel for approximately two feet. The mass was enucleated from the root of the mesentery, and the adherent small bowel was resected. A primary small bowel anastomosis was performed; no drains were placed. The patient did well after surgery.

Pathologic studies demonstrated a mesenteric tumor consisting of innumerable, thin-walled, vascular-lymphatic spaces surrounded by dense fibrous tissue stroma (Fig 2). Over a small region the lesion appeared to be attached to the small intestinal wall (Fig 3). Centrally, the lesion was entirely necrotic and acutely inflamed, representing an abscess cavity. No evidence of smooth muscle proliferation was noted. The lesion was therefore a large mesenteric lymphangioma, containing a centrally necrotic abscess cavity. Culture of the purulent fluid grew *Staphylococcus aureus*, which was coagulase positive and nafcillin resistant.

DISCUSSION

A mesenteric cyst discovered during an autopsy was first reported in 1507 by Beneviere, a Florentine anatomist.¹ Godart² has proposed the most widely accepted explanation of its origin. During ontogenesis, primordial lymphatic spaces develop from clefts in the venous plexus mesenchyme. These

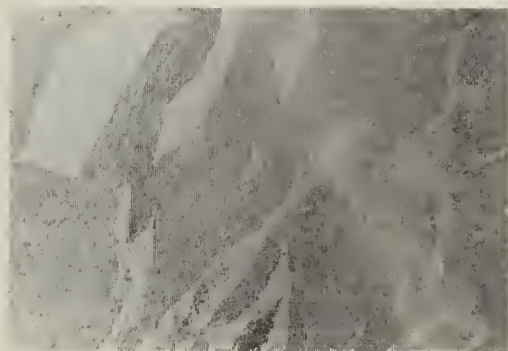


FIGURE 2. Endothelial-lined spaces within fibrous background. Several of the spaces contain red blood cells (hematoxylin and eosin stain, original magnification $\times 40$).

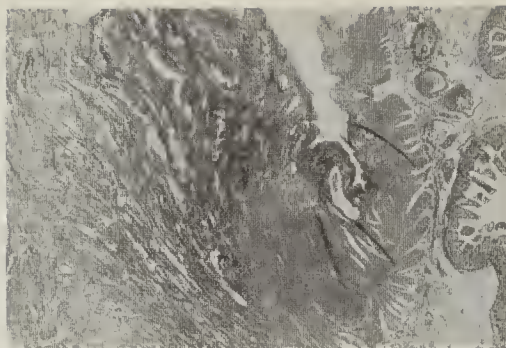


FIGURE 3. Small bowel with attached lymphangioma; lymphatic space within a fibrous stroma and adherent to the muscular wall of the bowel (Trichrome stain; original magnification $\times 20$).

eventually decrease in size since they are interconnected with the central lymphatic system. If there is failure of communication of a section of these lymphatic spaces, the lymphangioma or cystic hygroma will form.²

Histologically, cystic lymphangioma have endothelial lining foam cells and a wall containing small lymphatic spaces, lymphoid tissue, and smooth muscle. Lymphangiomas can be differentiated from mesenteric cysts; in the latter, the lining cells are cuboidal or columnar, and the walls lack smooth muscle and elements of the lymphatic system.³ Malignant forms of this tumor have been reported. They are usually sarcomas since all the cellular elements are of mesodermal origin.⁴

Lymphangiomatous cysts are rare clinical entities with an incidence of approximately one in 100,000 hospital admissions.^{4,5} Cysts can become clinically apparent at any age.⁶ Burnett et al⁷ noted that of 200 cases, 25% were in patients less than ten years of age, 5.5% were under one year of age, and 75% occurred in patients older than ten years, with a peak incidence in the fourth decade of life. A predominant 2:1 female/male ratio has been noted, and there is no predisposition in any racial or ethnic group.⁴

The most frequent location is the mesentery of the jejunum and the ileum, mostly in the mesenteric root.⁸ The cysts are found in every segment of the bowel, including the rectum, and have also been described in the submucosal position.^{9,10} A review of 57 case reports in the medical literature from 1951 to 1981 found that the most commonly reported anatomical position of these cysts is the mesentery of the small bowel (47%), followed by the omentum (23%).⁴

Symptoms induced by cysts in the mesentery are variable. The cysts frequently present as slowly enlarging, painless abdominal masses. Tillaux,

who first successfully operated to remove a mesenteric cyst in 1880, described a palpable mobile mass that easily shifts from the right to the left flank because of its mesenteric attachment.^{4,11} Warfield¹² similarly described an abdominal tumor, which was rounded, smooth, nontender, and very mobile, especially in the transverse direction. The review by Caldarola and LaDuca⁴ found that 61% of the patients had a palpable mass, whereas 30% had complained of pain. Diarrhea was seen in 16%.⁴ In a series of 20 patients described by Takiff³ in 1985, abdominal pain was the most common presenting symptom. Rupture and hemorrhage usually follow trauma, but may occur spontaneously. When the cyst compresses the bowel lumen by external pressure, partial or complete intestinal obstruction results. These cysts have presented as a chronic, intermittent intestinal obstruction and can conceivably produce a malabsorption syndrome because of the diarrheal state associated with partial bowel obstruction.⁵ Daniel¹⁰ described a case that mimicked acute appendicitis. Takiff described febrile clinical presentation and a purulent cystic fluid that grew *Escherichia coli* in a child with a large multi-cystic thoracoabdominal lymphangioma and preoperative pneumonia. Cheskis¹³ suspected a chronic illness when a low-grade fever resulted from suppuration within the cyst. This latter patient presented with an acute abdomen with sepsis and a large abdominal mass that extended into the pelvis.

The differential diagnosis includes ovarian cyst, pancreatic cyst, pedunculated uterine fibroid, hydronephrosis, hydrops of the gallbladder, retroperitoneal tumor, mobile kidney, and enlarged spleen.⁴ The optimal treatment for mesenteric lymphangioma consists of complete excision of the cyst and, when necessary, segmental bowel resection with wedge resection of the portion of the mesentery containing the cyst.⁵ Mortality rates are roughly 2% for enucleation alone and up to 15% with bowel resection. The patient described here underwent enucleation of the abscessed mesenteric lymphangioma in the root of the mesentery and segmental resection of the attached small intestine.

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Colonic urticaria in a case of adynamic ileus of the bowel

A unique radiographic presentation

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A specific hypersensitivity reaction reported as "colonic urticaria" has been reported several times in the medical literature.¹⁻⁹ Urticarial reactions have usually been diagnosed secondarily, either at postmortem or during the work-up for gastrointestinal symptoms such as pain, constipation, diarrhea, or bleeding. Urticaria of the colon itself has not been cited as the cause of bowel obstruction or symptoms unless accompanied by other pathologic entities such as carcinoma, volvulus, diverticulitis, or ischemia. In this case report, we describe a patient who presented with an ileus and urticaria of the colonic mucosa, the cause of which was ingested seafood.

CASE REPORT

A 55-year-old man presented in the emergency room with a chief complaint of constant generalized abdominal pain of two-days duration. This was associated with nausea and vomiting of ingested food. He reported no flatus or bowel movement for the previous 48 hours.

This patient stated that he had been in his normal state of health until this episode. He gave a history of ingesting raw clams and shrimp a few hours prior to the onset of his symptoms. He rarely ate seafood and had never eaten raw shellfish before. He had no known allergies to foods or medications, and his medical history was negative, except for an uneventful appendectomy 40 years prior to admission.

On physical examination, the abdomen was markedly distended and tympanic. There were high-pitched bowel sounds and tenderness to palpation in all four quadrants. There was stool in the rectal ampulla

that tested negative for blood. There was a well-healed scar in the right lower quadrant. No cutaneous pathology was noted, such as a rash or hives.

An upright abdominal radiograph revealed a markedly dilated ascending and transverse colon, with no air fluid levels. The left colon did not visualize, and there was no gaseous pattern noted in the small bowel (Fig 1). Routine hematologic and chemistry studies were all within normal limits. There was no eosinophilia.

A double air contrast barium enema was performed. The colon filled without evidence of obstruction, volvulus, carcinoma, or diverticulitis. There was marked submucosal edema and dilation of the ascending and transverse colon. The edema exhibited a pattern of large, round, polygonal raised plaques (Fig 2-4).

The patient was treated by bowel rest, internal decompression with a nasogastric

tube, and appropriate fluid and electrolyte management. He responded well to conservative therapy and became asymptomatic over a 24-hour period. He continued to improve clinically and was discharged home tolerating a regular diet with normal bowel function.

Prior to discharge, on hospital day four, colonoscopy was performed. The colonoscope was easily passed into the the ascending colon. There was no sign of obstruction noted. There was a region of submucosal edema noted in the splenic flexure which was slightly erythematous with raised patches of mucosa. The remainder of the colon had an otherwise normal architecture. No biopsies were performed.



FIGURE 1. Upright abdominal radiograph demonstrates dilated ascending and transverse colon. The left colon was not visualized.



FIGURE 2. Barium enema demonstrates complete filling of the colon without evidence of obstruction, diverticulitis, carcinoma, or volvulus.



FIGURE 3. Barium enema with air contrast demonstrates marked submucosal edema in ascending and transverse colon.

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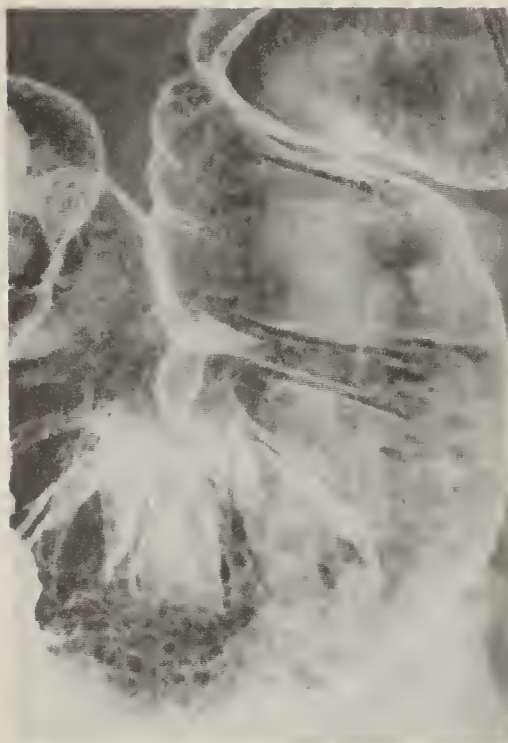


FIGURE 4. Proximal transverse colon demonstrates large round and polygonal raised plaques.

The patient was followed weekly in the clinic. A follow-up barium enema performed four weeks after discharge demonstrated a completely normal colon with resolution of the submucosal edema and plaques (Fig 5).

DISCUSSION

In 1940, Gray et al¹ were the first to report that colonic membranes can be passively sensitized by the intramucosal injection of reagin-bearing serum. This demonstrated that an aller-



FIGURE 5. Follow-up barium enema after four weeks demonstrates complete resolution of colonic edema.

gic reaction can be induced within the colonic mucosa. The first case of colonic urticaria was reported in the literature by Clemett et al,² who suspected urticaria of the colon in a patient who had a hypersensitivity reaction to penicillin. The term "colonic urticaria" was created to represent a characteristic mucosal appearance of a mosaic or polygonal nature. This pattern of the colonic mucosa has been described as sharply outlined; discrete polygonal areas; or as flat, reticulated, discrete plaques.

Berk and Millman³ were the first to describe this phenomenon with histologic confirmation in a patient post mortem. Yousefzadeh and Teplick⁴ presented an extensive review of five patients who presented with urticaria of the colon. A majority of these cases were associated with a hypersensitivity reaction to antigens related to prescribed medications. Seaman and Clements⁵ documented an additional six cases of colonic urticaria clearly not related to a hypersensitivity reaction, but rather associated with other pathologic causes such as carcinoma, volvulus, ischemic colitis, and Crohn's disease. Inflammatory lesions such as herpes zoster presumably can alter membrane permeability, with subsequent submucosal edema. Menuck et al⁶ reported two patients with herpes zoster with a mucosal pattern in the cecum strikingly similar to the urticarial pattern reported in the above cases. Greenberg et al⁷ described three examples of a similar mucosal pattern. One patient was diagnosed as having a cecal volvulus, and in two patients the mucosal changes were noted proximal to an obstructing carcinoma. The French literature reports two additional cases of urticaria of the colon.^{8,9}

Whether the cases are truly urticaria, or rather a nonspecific pattern of submucosal edema has been the topic of much discussion.⁵

It is well established that mucosal ischemia occurs proximal to an obstructing lesion. It has been postulated that such mucosal ischemia and edema might be responsible for this phenomenon. Through experimentation, Schwartz and Boley¹⁰ demonstrated that raising the intraluminal pressure in the gut results in a drop of mesenteric blood flow to 20–25% of the normal resting value. Mucosal edema may follow this decrease in mesenteric blood pressure, and may be responsible for the pattern of mucosal plaques seen in these patients.

In the case presented here, an ileus probably developed secondary to the ingestion of seafood. This ileus led to distention of the colon, creating an increase in the intraluminal pressure. This altered pressure gradient in turn led to the development of submucosal edema, which has been described in the medical literature as colonic urticaria.

The lack of substantial findings during the colonoscopy may be attributed to the fact that it was performed several days after admission. During this time, the bowel was at rest, and there was resolution of most of the submucosal edema, which had been seen on the barium enema.

The term colonic urticaria may be an inappropriate medical description of the colonic mucosal findings in these patients. A majority of the cases reported in the literature do not present substantiating evidence for a hypersensitivity reaction as the cause of the mucosal patterns. These colonic changes may be due to a variety of pathologic conditions. When they are seen radiographically, one can only postulate that the colon was subjected to a change in its normal pressure gradient. Unless the underlying pathologic disorder is otherwise fatal, these mucosal changes usually resolve with bowel rest and elimination of the causative factor.

Acknowledgments. The author thanks Dr John T. Flynn, of the Department of Medicine at The New York Infirmary-Beekman Downtown Hospital, for assisting in the reproduction and enlargement of the radiographs into photographs.

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Address correspondence to Editor, New York State Journal of Medicine, 420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication after editorial review. All letters are personally acknowledged by the Editor.

Animal experimentation for medical research

TO THE EDITOR: I have been following the exchange between Dr Fred Rosner, Chairman of the Committee on Bioethical Issues of the Medical Society of New York State, and Dr Stephen Kaufman of the Medical Research Modernization Committee (MRMC).¹⁻⁴ As MRMC Chair, I feel I should contribute to the dialogue.

I agree with Dr Kaufman that, along with a small but prominent group of physicians, Dr Rosner has not concealed his staunch advocacy of animal research. This being so, the degree of objectivity he brings to the debate must be questioned. He certainly has every right to believe that, in opposition to animal rights philosophy, the moral position is to use animals in biomedical research "for the benefit of mankind." He does not have the right, however, to assume that the only ethically acceptable position is one which favors animal use.

Dr Kaufman has clearly stated the MRMC position that animal experimentation can cogently be opposed on scientific, medical, and health related grounds. If proponents of animal research such as Dr Rosner take exception with this position, let them do so in a scholarly and scientific fashion. The fact that they rarely do so leads one to believe that they do not have the requisite facts.

I can offer many examples to refute Dr Rosner's contentions, but limited space allows me only two. Many world renowned cancer researchers have concluded publicly that animal research is not the direction to follow in the quest to conquer this dread disease. Professor Umberto Veronesi, Director General of the National Cancer Institute, President of the European School of Oncology, and Scientific Director of the Foundation for Cancer Education writes: "... research has passed from work conducted on laboratory animals to work involving human tumor cells, thanks to new in vitro 'techniques.'"⁵ In addition,

Dr Renato Dulbecco of the Monoclonal Antibody Laboratory of the Armand Hammer Cancer Center/Salk Institute writes: "If we wish to understand human cancer, the (research) effort should be made in humans because the genetic control of cancer seems to be different in different species."⁶

In addition, the identification of methods to prevent heart disease has had nothing whatsoever to do with animal research, the results of which can only mislead and obfuscate. Consider the risk factors. Animals do not smoke; smoking is one of the major risk factors. The cholesterol issue cannot be studied in herbivores because they ingest no cholesterol, and carnivores, such as the dog, do not suffer cardiac damage regardless of the amount of cholesterol they ingest.

Dr Rosner, let us drop the "humane treatment of laboratory animals" rhetoric and really discuss the merits of animal experimentation.

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In reply. Dr Cohen challenges me to support my advocacy of animal research "in a scholarly and scientific fashion." Perhaps Dr Cohen failed to read the section in our article¹ dealing with the benefits to mankind that derived from animal experimentation. We pointed out the 1988 glossary prepared by the Council on Scientific Affairs of the American Medical Association. This cites review articles,

which reference more than 800 original scientific manuscripts that delineate medical advances that were dependent on the use of experimental animals.²

Dogs were used in the classical experiments of Banting and Best that identified insulin as an important hormone in the treatment of diabetes. Procedures for transplantation of the pancreas and other organs were developed using dogs and other animal models. The world's first hepatitis-B vaccine depended on research with chimpanzees and other primates, since the virus cannot be transmitted to other laboratory animals. Dogs have been used to study rickets and calcium and vitamin D deficiency. Dogs have also been used to develop effective therapies for common human ophthalmological disease such as glaucoma, cataracts, and uveitis, which also occur in dogs. The pump oxygenator used during heart lung operations was developed using dogs. The dog was an important animal model for the development of the use of hypothermia in prolonged neurosurgery and for many cardiovascular advances. Yet, in spite of all the aforementioned, Dr Cohen states that "carnivores such as the dog, do not suffer cardiac damage regardless of the amount of cholesterol they ingest," a total nonsequitor.

Dr Cohen accuses me of assuming "that every opposition to animal use derives from ethical considerations." These are his words. I never made such an assumption. Dr Cohen offers two examples to refute my contention that animal research for the benefit of mankind is not only morally justifiable but scientifically and philosophically correct. Professor Veronesi's article does not speak against the use of animals for medical research. In fact, much of the work cited by him about "new chemical, and endocrinal pharmaceuticals" including interferon, interleukin, and monoclonal antibodies uses animals as research models.³ Dr Dulbecco discusses his belief that major emphasis in cancer research should be devoted to the sequencing

of the cellular genome. The sequencing of the human genome must obviously be done in humans. However, Dr. Dulbecco does not speak against the use of animals for medical research when such use is appropriate and no alternate methodologies exist.⁴

The medical community has always and continues to promote the humane and appropriate use of research animals and attempts to explain to the public and legislators the importance of animal research to medical progress.³ The medical community deplores the increasing vigor, and often violent efforts, of those who claim to be more concerned with the humane treatment of animals than those who are involved with advancing the cause of human health.⁴ There is little doubt that animal experimentation is being threatened by well-financed, well-organized, vocal and often violent animal rights groups.⁵ The medical community "must not only defend the appropriate use of animals in biomedical research but we must actually promote such use, through education. . . ." I endorse the appeal of the American Medical Association to American physicians and scientists to assume a primary role in defending the use of animals for biomedical research.⁶

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Possible mode of transmission of nosocomial infections

TO THE EDITOR: It has occurred to me that the cuff of the sphygmomanometer may well be one of the overlooked

methods of transmission of nosocomial infections. I have noted that there is usually a metal basket attached to the wall, at the head of the hospital bed which contains sphygmomanometer and cuff. This same cuff is used several times daily on the patient, regardless of the diagnosis, and when the bed is vacated, the same possibly contaminated cuff is used on succeeding patients ad infinitum!

I have never observed any special sterility precautions taken to prevent cuff contamination. It would be interesting to receive other viewpoints on this subject.

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In reply. Noncritical items such as blood pressure cuffs are not generally considered to be involved in disease transmission.^{1,2} Because blood pressure cuffs usually come in contact with intact skin which is not a portal of entry, no special precautions appear to be necessary. If the cuff is visibly soiled with blood or body fluids, it should be cleaned or if this is not possible replaced.^{1,2}

In a classic series of experiments done in the 1950s by Perry and Rammelkamp, it was demonstrated that recruits in army barracks who were issued freshly laundered, streptococcus-free blankets acquired strep infection or colonization just as frequently as those issued highly contaminated blankets.³ This observation was later linked to the dry state of the organisms when strep contaminated dust moistened by inoculation with secretions caused infection⁴ and the same mixture after four to eight hours of drying did not.⁵ This lack of association between the dry environment and nosocomial infection was more recently confirmed by Maki et al.⁶ Maki's infection control team took the opportunity of their hospital's move from a 56-year-old building to a new facility to culture the air and environmental surfaces in each plant. Despite major differences in environmental contamination between the old and new hospitals, the incidence of nosocomial infection remained unchanged.

Most preventable nosocomial infections can be traced to invasive procedures where sterility precautions are both in order and usually effective. Unfortunately when we focus on un-

likely sources of potentially preventable nosocomial infections, we miss an opportunity to identify the real causal factors. Nevertheless, science notwithstanding, one manufacturer has actually produced a disposable blood pressure cuff.

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The physician's home—An act of grace

TO THE EDITOR: All too often in our dash through life, we fail to pause and savor the good things at our doorstep. For years, we paid our membership dues to the Society and also included money for the Physician's Home. Once we asked where it was, and they told me that it was no longer a home but a fund for helping needy physicians and their families.

The answer was sufficient until the late Mrs Anne Secky of the Queens Auxiliary, and a staunch member of the Board for the Physician's Home, asked me to join the "Board." Having resolved to hold off on future committee appointments, I began my refusal. Reading me all to well, she began to cry softly. Helpless before such emotion, I readily agreed.

Some time later, we were sitting around a table and listening to what happens to wives and children when fellow physicians become seriously ill or die. The contents of their letters were profoundly moving and their appreciation for the efforts of the "Home" was truly gratifying. It inspired the physician and auxilian members and their one person staff to redouble their efforts. The curious

thing was the dedication of the banker, the money manager, and the accountant who were present. They were so delighted to be participants in this remarkable undertaking.

One leaves those meetings with a feeling of shared wonder. For that brief moment, we have put aside our axes, helmets, and shields. We have reached out to help fallen comrades and have been ennobled by the act. Thank you, Anne Secky.

RANDALL D. BLOOMFIELD, MD
Past President
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County of Kings

The responses of radiologists to referring physicians: A classification and description

TO THE EDITOR: Physicians of all specialties and in all phases of their training and practice depend upon radiologists for consultation and for interpretation of radiographs. The radiologist's intent is to help those in need as expeditiously as possible, in a comprehensive manner and with a style that leaves the consultants gratified with their enhanced understanding and ability to approach their patients' dilemmas.

Daily radiologic practice involves being seated in front of a viewbox surrounded by mountains of films requiring interpretation. Therefore, it is the back of the radiologist that first greets consultants. They must usually initiate the dialogue and attract the radiologist's attention. We have observed several different approaches used by physicians to achieve this. On the basis of our observations, we have classified physicians seeking consultation into five types.

Type I individuals are generally nonaggressive and usually are not

from a surgical specialty. They might very well be medical students or interns. They are benign and noncombative and will generally stand behind the radiologist, not making the slightest noise. The radiologist, in fact, may not even know anyone is there. This is the type of person who is a pleasure to assist.

Type II individuals are generally more aggressive, but only slightly so. The radiologist knows that they are standing behind by the ruffling of a radiograph or film folder. They never utter a word but occasionally make sounds such as sniffing, in an attempt to get attention. When one turns around, they may or may not be there.

Type III individuals are much more aggressive. They also stand behind, but have a number of ways to let the radiologist know of their presence. A radiograph may conveniently fall and slide beneath the feet, or land on top of the pile of films currently being read. At times, the entire folder may end up on the reader's lap. These persons generally succeed in getting undivided attention, hopefully without causing any bodily damage.

Type IV individuals can be both intrusive and rude. They suddenly come upon the helpless radiologist, bumping the chair and flinging films in all directions with a razor sharp precision. The noise from rattling films and their intrusive conversation make it difficult to continue one's dictation. These individuals will not cease in their efforts unless they are immediately noticed. The working radiologist has no choice but to turn around or be persecuted.

Type V individuals are what could be referred to as the seasoned veterans. The radiologist is at their mercy, and all exits are immediately sealed shut. If an ongoing attempt is made to dictate, they will shut off the machine

and if necessary remove the tape or handpiece. The Dictaphone[™] and viewbox belong to them. If a radiograph is on the viewbox they will remove it, or even place their own film on top, causing what we call the "pseudo-double exposure phenomenon." They require an immediate response yesterday, and, if necessary will seek out department chiefs and hospital administrators to achieve their goal. In fact, they will probably leave the room with the film dictated, transcribed, and officially reported in the patient's chart before leaving the radiology department.

This classification has been devised as a satirical response to real life situations that occur daily in radiology departments, and represents only a sampling of the different types of physicians with whom we come into daily contact. We try to respond to everyone in a timely and efficient manner, give accurate interpretations, and have our medical colleagues walk away content. Most often we succeed and manage to remain both physically and mentally intact. Pardon our backs.

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ERRATA

The June 1990 issue of the *Journal* contained two errors. Line 33 of page 235 should read "Harlem community" not "Harlem illnesses."

Table 1 on page 243 has erroneous data. Under the "Discouraged" column, the "Number" and "Percent" for "Other (friend, neighbor)" should be 124 and 40, respectively.

A history of American public health

The Sanitarians: A History of American Public Health. By John Duffy. 300 pp. Champaign, IL, University of Illinois Press, 1990. \$32.50 (clothcover).

Duffy's narrative history of American public health encompasses four centuries of dealing with epidemics, plagues, and various scourges intermixed with the ebb and flow of social, political, and economic changes in the United States. To delineate the historical scope, Duffy defines public health as "community action to avoid disease and other threats to the health and welfare of individuals and the community at large" and public health policy to promote health rather than simply maintain it. Obviously, public health is much more than the control of communicable diseases and sanitary measures. Pointedly, the subtitle of this book, "A history of American public health" is more accurate than "The Sanitarians." If "health is wealth," public health is money in the bank.

Starting with the early settlers in the 1600s to the present time, public health workers, physicians, and citizens gallantly battled the invading epidemic and endemic hordes such as Asiatic cholera, diphtheria, gastroenteritis, hepatitis, hookworm, influenza, leprosy, mumps, pellagra, poliomyelitis, malaria, smallpox, syphilis, tuberculosis (TB), typhoid, and yellow fever. Weapons in the encounters included quarantine, sanitation, drainage systems, pure drinking water and food, improved nutrition, decent housing, inoculation, vaccination, and public health education. Today's scourges go by different names such as nuclear waste disposal, chemical and occupational exposures, air pollution, stress reduction, alcoholism, and substance abuse.

Combining the ever present health threats with the human responses gives rise to truths that are stranger than fiction. If you like a good story, if you like docudrama, if you like to read about heroes—Duffy's book is for you. Almost every page contains high drama based on comprehensive research, illustrated with pertinent quotes, and Duffy's insightful analyses.

Throughout the history of American public health, a constant and extraordinary motif is the fluctuation between apathy and frantic reactions to periodic health crises. In the American colonial era, smallpox and yellow fever got the most attention even though malaria, respiratory infections, and enteric diseases caused the most illness and mortality. In the 19th century, TB took a back seat to the spectacular epidemics. Today the AIDS crisis, influenza outbreaks, Legionnaire's disease, and other dramatic problems overshadow the long-standing carnage inflicted yearly on our highways in automobile accidents and the need to effect changes in lifestyle to reduce mortality from the major killers in America—heart disease, cancer, and stroke. Former Secretary of Health, Education, and Welfare Joseph Califano said: "American people are killing themselves by carelessly continuing unhealthy personal habits,

by carelessly polluting the environment, and by permitting the existence of harmful social conditions such as poverty, hunger, and ignorance." It appears as if certain events become acceptable as part and parcel of the trials and tribulations of everyday living. Duffy says: "Whether or not familiarity breeds contempt, it certainly breeds acceptance."

Another recurring theme in American public health history is the impact of acculturation on disease and death. Newcomers to the cities included white farmers, Southern black sharecroppers, poverty stricken Irish, Eastern European peasants, impoverished Latinos, and refugees from Viet Nam. All had to be taught to survive in an urban environment. People of diverse cultures are rapidly integrated into mainstream society, but the ensuing population density creates sanitary and environmental problems with each new wave of immigrants from within or without the United States.

Another persistent theme throughout the years is the fight to replace ineffective traditional methods with more effective ways to maintain health. Human nature tends to stick to tried and true habits and to be wary of new procedures. People are reluctant to cast aside traditional remedies or preventive measures even in the face of existing emergencies. During the poliomyelitis epidemics of the 1950s, parents put camphor or garlic necklaces on their children to ward off the dread disease. This problem continues today as urban health workers display an insensitivity to cultural, religious, and language differences in matching therapeutic modalities and patients.

Zealous protection of individual rights engenders monumental difficulties for health officials in a democracy. American public health history is replete with constant clashes between individual liberty and the public welfare. "Industry's befouling of the environment became almost a God-given right, for government interference in business had always been considered on a par with interference in citizens' personal lives." Inevitably, sanitary and health regulations do infringe on American concepts of rugged individuals, as do all laws and ordinances. According to Duffy, "the number of deaths from drunken driving would be much lower if the average American did not consider driving a right rather than a privilege." In the 1930s, Dr Fred L. Soper persuaded Central and South American government leaders to allow inspectors to enter all homes and businesses to inspect and spray for *Aedes aegypti* mosquitoes to eliminate yellow fever. Eradication procedures moved smoothly until reaching the US where the activities abruptly halted. Dr Soper attributed this failure to the inability of American government, at any level, to provide entry into private premises to search for mosquitoes. Gradually, the mosquitoes reinfiltated from the US into Latin America.

Casual observers of American medicine can see commonplace evidence of the constant public health history themes

of civic apathy and crises reactions, acculturation, effective mechanisms replacing the ineffective, and the clash between personal liberty and general welfare. These persistent themes interact with three factors to determine public health policy: prevailing medical concepts first and foremost, prevailing social attitudes, and economics. Replacing concepts of miasma toxins by microorganism causation resulted in changed preventive procedures. If social attitudes hold that sexually transmitted disease, syphilis and AIDS, are the result of sinful living, society has little inclination to try to cure or prevent them. Economically, the public usually supports spending tax money to resolve an immediate health crisis. However, the public's short memory may raise obstacles to appropriating funds for long-term preventive measures.

Starting with the early colonial years of growth and expansion, Duffy moves on to the emergence of health boards and into the sanitary movement and the reformers of the early and mid-1800s. After the Civil War innovations, public health became institutionalized as municipal and state boards of health flourished. In addition, hospitals and the federal government entered into public health activities. In the late 1800s and early 1900s, bacteriology revolutionized and created the new practice of public health with powerful state entities and even rural programs. With the great depression of the 1920s and 1930s and the war years of the 1940s, 1950s, and 1960s, health reforms surged under the federal government's stimulation. Today's shrinking and changing world is again developing another new public health wherein demographics, long-term care, and high technology are major actors.

Colonial life in America was fairly grim. "Epidemic and endemic disorders flourished, infant mortality was high, and death was always close at hand . . . colonial towns were odorous and lacked effective water, sewer, and street cleaning systems." By the mid-1800s, conditions had not greatly improved. On April 28, 1848, the *Pittsburgh Daily Gazette* reported that a young woman attempted suicide by jumping into a local canal, but the water was so bad that she quickly climbed out. She considered jumping in again but after "beholding its filthy condition, and inhaling its foetid odor, she concluded to postpone drowning until she could meet with cleaner water." At this time, most educated Americans still believed that "poverty and immorality went hand in hand and that cleanliness was next to godliness. The laws of nature and God were the same, and those who deviated from them paid the price in poverty, disease, and death."

Perhaps contrary to common perceptions of the medical profession as extremely conservative, individual physicians were among the leaders of the early health and social reform movements. Physicians initiated the sanitary movement, and in the late 1800s, they helped organize most of the citizens' sanitary associations. Professional medical organizations strongly supported all public health measures. New York City's Academy of Medicine through its Committee on Public Health fought to establish the Metropolitan Board of Health, investigated a wide range of issues, was politically active, and constantly prodded the membership to take a stand on social issues. Committee members included the leading health reformers in the city.

In 1873, the first significant American professional public health journal emerged. Under the editorship of Dr A.N. Bell of New York, *The Sanitarian* was published. In addition to medical subjects, Dr Bell aimed to discuss "the

practical questions of State Medicine" such as the health of the armed forces, marine health, quarantine, civic cleanliness, the food supply, occupational health, and other topics. Furthermore, Dr Bell announced that he would accept no advertising "of even questionable character." At that time, newspapers frequently published paid ads touting the cures of health care practitioners without regard for the validity of the claims. For the next 30 years, Dr Bell's journal published articles covering social issues of consequence including sanitary topics, sweatshops employing women, the health of blacks, and child labor. Although both the American Medical Association and the American Public Health Association avoided the subject, Dr Bell printed articles on venereal disease. Dr Bell's journal was followed by *The Sanitary Messenger* (1878), *The Sanitary Engineer* (1880), and *The Sanitary News* (1882).

In 1870, the St Louis city council passed the Social Evil Ordinance and became the first United States city to deal with the problem of prostitution and venereal disease. This law provided for the licensing and medical inspection of prostitutes. Infected women were sent to the Social Evil Hospital funded by the license fees collected from brothels and individual prostitutes. All of this caused quite a stir throughout the nation, and for the first time medical journals discussed the subject at length. Locally, the St Louis medical society gave its tentative support. In 1874, the state legislature reacted to pressure and repealed the law. Regulation of bawdy houses was fully supported by the St Louis Board of Health, which deplored the hasty repeal of the law. However, the "purity movement" was all powerful and "little would be done about venereal disease until well into the 20th century." In fact, when Dr Thomas Parran was New York State Commissioner of Health in the 1930s, he gave a radio talk on venereal disease. Dr Parran was warned by the radio announcer that if one person telephoned in to protest, he would be cut off the air. Fortunately, there were no calls. When Dr Parran became Surgeon General of the United States Public Health Service, he insisted that national radio networks and news services use the word syphilis instead of a euphemism. In 1938, Parran pushed Congress to enact the National Venereal Disease Control Act, which appropriated \$3 million in matching grants to the states.

Considering the current reputation of hospitals in the American health care system, it is appropriate to recall that the tremendous upgrade in prestige is essentially a 20th-century advancement. "For most of American history, hospitals were designed to care for the sick poor or for ill and destitute strangers. Respectable citizens expected to be born, treated, nursed, and allowed to die in their own homes." Paradoxically, home health care has burgeoned in recent years for cost containment and quality care reasons. Rich and poor alike regarded the hospitals as a place where the sick poor were sent to die. Incidentally, the two major claimants for the oldest US hospital are Charity Hospital in New Orleans (1736) and the Pennsylvania Hospital (1752). As late as 1795, only two hospitals functioned in the original colonies, the Pennsylvania Hospital and New York Hospital (1791). Although Congress passed an act to provide medical care for merchant seamen in 1789, the Marine Hospital Service did not establish its first facility until the beginning of the 19th century with hospitals in Boston and Norfolk.

It was while controlling communicable diseases that public health experts realized the need for educating the

public. In 1910, Dr Oscar Dowling became president of the Louisiana State Board of Health. He immediately proposed a traveling health exhibit to bring information to every community with a railway station. A local railroad company lent an engine, an exhibit car, and a housing car for the staff. In six weeks, the train went from New Orleans to the Shreveport state fair. Exhibits included literature on hygiene, pathological specimens from tuberculosis cases, enlargements of flies' feet, data on hookworm disease, a model of a sanitary privy, model school desks, and displays on food, nutrition, dental care, dairies, and dairy equipment. In the next seven months, the health train made 256 stops covering 7,000 miles. At each stop lectures were given on hygiene, inspectors inspected dairies, stores, restaurants, food processors, and public buildings. Milk, water, and foods were tested, and garbage and sewage disposal were rated. On the basis of his observations, Dr Dowling "blamed Louisiana's high incidence of sickness and disease on ignorance and apathy." This health train received nationwide publicity and was invited to visit other states. Dowling's traveling health exhibit continued until 1928 when he "fell afoul of Huey P. Long."

To reinforce the maxim that history repeats itself, the physical fitness movement is not unique to this day and age. During the reform period of the 1830s and 1840s, diet and exercise were emphasized for the first time. There were numerous gymnastic clubs and societies that immigrant populations brought with them from Europe. Late in the 19th century, there was another movement in conjunction with the dietary requirements of the Seventh Day Adventists and the appearance of the bicycle. In the 1920s, Bernarr McFadden was a guiding force in physical fitness. Today, we have jogging, work-outs and assorted variations. Duffy questions the commercialization of the fitness movement: "To sell vitamins, health foods, weight-loss pills, exercise machines, and home air and water purifying devices, the manufacturers must first convince prospective customers that their health is in jeopardy." A deluge of advertising is found in newspapers and on radio and television. Speaking of the omnipresent dangers from insecticides, industrial wastes, nuclear radiation, and environmental threats. "Unable to differentiate between valid warnings and lurid reports of unseen and unfamiliar dangers, small wonder that so many Americans today worry about their health."

Since the 1930s, American public health history indicates two major themes: a steady fragmentation of health services and the expanding role of the federal government. It has been estimated that about 80 different government agencies participate in health services with leading roles being played by the Veteran's Administration, the Department of Defense, health and welfare departments, mental health units, and so on. This fragmentation is reflected on

private voluntary health and philanthropic organizations as well. As to expansion of the federal government in the health area, it is reasonable to ask why since the US Constitution does not mention the word health and no major committee of Congress has health in its title. Federal government expansion came about mainly through its power to appropriate monies, to regulate interstate commerce, and to provide for the general welfare. Today, Medicare and Medicaid alone spend more than \$100 billion for health care services to say nothing of the rules and regulations enacted regarding the delivery of such services. In spite of attempts to initiate rational health planning procedures, fragmentation and federal expansion continue unabated.

In concluding, Duffy points out that "medicine played little part in the rise and fall of the great killers of earlier days." Bubonic plague disappeared from Western Europe in the 17th and 18th centuries, typhus began its decline at the same time, TB declined well before the discovery of effective chemotherapy, malaria was already limited by the time the role of the anopheles mosquito was recognized. A prominent researcher attributes the major declines in morbidity and mortality to three factors: improved nutrition, improved housing, and improved sanitation.

In commenting that nationwide public education campaigns can have a major effect today, Duffy identifies areas of concern as obesity, alcoholism, substance abuse, venereal disease, and auto safety. He illustrates this point by noting that former Surgeon General Everett Koop provided considerable impetus in his educational activities regarding AIDS prevention and smoking cessation.

John Duffy is the author of a two-volume history on public health in New York City and a history of American medicine. His painstaking scholarship and attention to detail results in a treasurehouse of information on every page of his books. *The Sanitarians* is highly recommended and should assist physicians and others to establish their links to medical activities and programs that we take for granted today such as vaccination, well baby stations, pure food and milk, and safe water. In addition, New York can take pride in the vision and innovations of a large number of American public health pioneers who came from this state.

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No-fault malpractice: Sweden

The malpractice insurance crisis in the United States has given rise to calls for an end to reliance on the tort law system for compensating the victims of medical injuries. Under the tort system, the injurer pays the victim on the basis of fault, which must be established in court. Thus, patients who feel they have been harmed in the course of medical care must prove a causal relationship between the actions or negligence of the practitioner and the particular injury that occurred. Critics of the status quo seek mechanisms that would spare patients and practitioners the tribulations of the tort claims process and at the same time assure those injured in the course of receiving medical care that they receive fair compensation for pain, suffering, and economic losses. Suggested reforms have emphasized the welfare of the victim over the culpability of the provider and consequently have been described as "no-fault" systems. Proponents of these solutions often cite the medical injury compensation schemes of Sweden and New Zealand as possible alternatives to the tort liability system. This article describes the Swedish approach. A discussion of New Zealand's system will appear in a subsequent issue of this publication.

Sweden: The Patient Insurance System

The very title of the Swedish mechanism for addressing medical injury indicates its emphasis on the welfare of the patient over the blameworthiness of the provider. The essence of the system is to pay compensation to the injured party if it was possible to have avoided the injury in question. The question of fault is irrelevant.¹ The Swedish patient thus is assured of compensation, regardless of whether his or her injury was caused by medical negligence, mismanagement or error.

In its rejection of fault as a determinant for the payment of compensation, the Swedish system also provides, in effect, liability insurance for the provider.² At the same time that it saves patients the task of initiating tort proceedings when genuine malpractice has occurred, the Swedish system spares providers the ordeal of defending themselves against questionable charges made for lack of alternative means of redress.

Compensation claims for medical injury in Sweden are received and reviewed by a consortium of insurance companies that administers the Patient Insurance System. In general, injuries eligible for compensation fall into five categories: genuine treatment injuries, diagnos-

tic injuries, accidental injuries, infection injuries, and injuries caused by diagnostic investigations.²

Within these five categories, there are certain injuries that are not considered compensable:

- treatment results that constitute natural and unavoidable consequences of the basic illness or its necessary treatment;
- injuries resulting from necessary and well-known risks;
- infection caused by the patient's own bacteria;
- psychic injuries which are not the result of bodily injury.

The Swedish system does not award compensation for every avoidable injury. To receive compensation, the injured party must report sick for at least 14 days, be hospitalized for at least 10 days, have suffered permanent disability, or die.^{1,3} As a result, Swedes must tolerate a fair amount of pain and inconvenience before their injuries, even when attributable to negligence or error, can be considered compensable. There seems an implicit recognition in the Swedish system that the patient can be compensated for the risks inherent in medical care only to a certain point, and that the costs to society of insulating the individual completely from such risks are prohibitive.

The Swedish system encourages the reporting of medical injuries. In hospitals, for example, there is an information sheet by each bed asking the patient to report any injury that he or she experiences. The system also encourages the reporting of injuries by attending physicians, assuring them that a decision to grant compensation to a particular patient will not be interpreted as a comment on the individual practitioner's competence or integrity.¹

The Swedish Patient Insurance System is a payor of last resort. All other sources of compensation must be exhausted before the system will make a payment to a successful claimant. Because Sweden's elaborate social welfare system pays for up to 90% of earnings lost because of illness or injury, the Patient Insurance System need not compensate successful claimants for such losses. Thus, fully 70% of all funds paid by the system are for pain, suffering, and loss of amenities.³ Any related costs for nursing care, medical treatment, or home care are paid by the country's national health insurance system.

The funding and administration of the Swedish Patient Insurance System blends public sector support and private sector management. The system is financed through per capita tax contributions from the country's 26 county councils (local governments). A small amount of additional funding comes from fees assessed on Sweden's few private practitioners. The system is administered by a consortium of four private insurance companies. The incentives for these organizations in managing a public sector program are the administrative fees,

economies of scale, and investment capital generated by so large an endeavor.

Administrative costs constitute 14% of the Patient Insurance System's budget; fully 86% goes to compensation. Indemnity fees are set in a fixed schedule and are adjusted for inflation annually.¹ The system will pay a maximum of approximately \$300,000, but the average total payment per claim is far lower—only about \$6,500.^{1,3} Large lump sums are rarely awarded, and even the more generous awards are paid in installments. Funds for ongoing care related to an injury (eg, lifelong home care) are also parceled out annually rather than in single payments on the basis of projected costs. Payments for pain, suffering, and loss of amenities are comparatively low, with maximum awards running about \$70,000.³ Over a 10-year period (1975–85), the average compensation for injuries occurring in hospitals was \$22,850.¹

The Swedish system, in comparison to other countries, appears to be an equitable one. Swedes who experience medical injuries that meet minimum review criteria are virtually guaranteed compensation from the Patient Insurance System. In the United States, compensation is awarded only to those patients with the tenacity and resources to persevere in the tort claims process. Although claimants in the United States might be dissatisfied with Sweden's comparatively low levels of compensation for pain, suffering, and loss of amenities, many injured patients, who currently file no claims at all, would likely prefer the imperfections of the Swedish system to the hit-and-miss results of the tort system.

As for the nature of claims paid, a comprehensive study of the first eight years of the Swedish Patient Insurance System (1975–82) found that 75.7% of the 61.5% of claims deemed payable were due to injuries resulting from medical treatment.² Of this 75.7%, a total of 44% were surgery related. This proportion is comparable to the 48% of adverse events in the Harvard study of New York State hospitals that were found to be the consequence of an operation.⁴

Fully 17.2% of the 61.5% of claims found compensable in the first eight years of the Swedish system were attributable to logistical causes (eg, slipping on the floor). Data for the first 10 years of the program (through 1985) showed a slight increase in the treatment category (77.8% of compensable claims) and a slight reduction in logistical causes (15.5%).¹

The Swedish Context

Sweden is a relatively homogeneous society whose population of 8.3 million is small compared with that of the United States. It is also a country that has an elaborate system of national health insurance, with the government as the principal provider of services. Most of Sweden's physicians are public employees, and the practices of the country's few private doctors are, with rare exception, confined to prophylactic and diagnostic activities.² Swedish health care is less personalized than in the United States, and patients are likely to be treated by the physician who happens to be on duty at the particular clinic or hospital.¹

Sweden also possesses an elaborate system of social security, resulting from an egalitarian political culture and a strong sense of public responsibility to assist those who suffer misfortune. It is also a society that has sought to make government responsive to the needs of the average citizen, a tendency best manifested in the Swedish origins of the ombudsman concept. The Patient Insurance System evolved in the 1970s as part of a series of official reforms and in response to growing consumer advocacy.¹

Given the difference in political cultures of the two countries, it is doubtful that malpractice reform would evolve in the United States for the same reasons that the Patient Insurance System came about in Sweden. Still, the Swedish in its workings which appear to be central to its efficacy include:

- the exclusion of minor injuries from coverage, to keep the system manageable and affordable, and to discourage the submission of frivolous claims;
- the distinction between natural, unavoidable outcomes of treatment and those that could have been avoided and which, therefore, justify the payment of compensation;
- the exclusion of injuries due to the known risks of certain procedures and treatments (This exclusion may be more difficult to effect in the United States, where we lack Sweden's elaborate safety net of national health insurance and generous social security);
- the use of the private sector to insure the system and manage its claims. This feature of the Swedish system might make no-fault palatable to those in the United States who would tend to view government involvement in health and insurance matters as socialized or anticompetitive.

No single system or model is likely to prove a panacea for the malpractice crisis. However, Sweden's experience provides a useful contribution to the debate over how to change our current approach to malpractice in a way that will provide fair compensation to the injured patient and reasonable protection for the conscientious provider.

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***Haemophilus influenzae* Type B Vaccination Update**

Recently, the US Food and Drug Administration licensed two new *Haemophilus influenzae* type b (HIB) vaccines for use with infants beginning at two months of

age: Diphtheria CRM 197 Protein Conjugate (HbOC), manufactured by Praxis Biologics, Inc, and Meningococcal Protein Conjugate (PRP-OMP), manufactured by Merck, Sharp and Dohme. A third HIB vaccine (Diphtheria Toxoid Conjugate, Connaught Laboratories) is available for use in children age 15 months and above. The American Academy of Pediatrics and the Immunization Practices Advisory Committee have recommended the use of these vaccines at the schedules recommended by the manufacturers. These new schedules represent a significant advance in the control of HIB disease because most of the morbidity and mortality caused by HIB occurs in children less than 15 months of age.

HIB is a common cause of serious systemic bacterial disease in the United States. It is the leading cause of bacterial meningitis in children under five years of age, accounting for an estimated 12,000 cases annually in the United States. In addition to meningitis, other forms of systemic HIB infection include epiglottitis, sepsis, cellulitis, septic arthritis, osteomyelitis, pericarditis, and pneumonia. The national mortality rate among severe HIB cases is 5% and a significant number of children suffer residual neurologic damage as a result of infection. By five years of age, one in every 200 children in New York State will have a serious systemic infection due to HIB.

There were 383 cases of HIB disease reported in New York State in 1989. Seventy-five percent occurred in children under five years of age and 161 (42%) were less than 12-months old. The age distribution of cases is shown in Table I. In 1989, three deaths occurred in children under five years of age.

Recommended Haemophilus influenzae Type B Vaccination Schedule

All children should be immunized with an approved HIB vaccine with the first dose at two months of age or as soon thereafter as possible. HIB immunization may be given at the same time as diphtheria, measles, mumps, rubella, and inactivated and oral polio immunizations. (Any of the vaccines may be injected in the thigh, and two injections may be given in the same deltoid.) All HIB conjugate vaccines should be administered via the intramuscular route. There are no known contraindications to simultaneous administration of any HIB conjugate vaccine with either pneumococcal or meningococcal vaccine.

TABLE I. Age Distribution of Haemophilus influenzae Type B Disease, New York State, 1989

Age	Reported Cases		
	NYS, Exclusive of NYC	NYC	Deaths
0-2 months	13	6	2
3-4 months	23	7	0
5-6 months	19	10	0
7-11 months	52	31	0
12-14 months*	40	7	0
15 months-5 years*	51	30	1
5+ years	39	55	2
Total	237	146	5

*Estimated based on distribution of cases age 12 months to five years with known date of birth.

TABLE II. New York State Department of Health Recommended HIB Vaccination Schedule

Vaccine	2 Months	4 Months	6 Months	12 Months	15 Months
HbOC (Praxis Biologics, Inc)	dose 1	dose 2	dose 3		dose 4
PRP-OMP (Merck, Sharp, and Dohme)	dose 1	dose 2		dose 3	

tions to simultaneous administration of any HIB conjugate vaccine with either pneumococcal or meningococcal vaccine.

The New York State Department of Health (NYS-DOH) recommendations for HIB vaccination, if begun by two months of age, are shown in Table II. The immunization schedule for children older than two months of age at the time of the first dose of HIB vaccine is shown in Table III.

Unimmunized children who experience invasive HIB disease when younger than 24 months of age should still receive an approved vaccine according to the age-appropriate schedule since many of these children fail to develop adequate immunity after natural disease. Unvaccinated children 15-59 months of age may be given any one of the three conjugate vaccines licensed for this age group.

Ideally, the same conjugate vaccine should be used throughout the entire vaccination series (according to the schedule outlined in Table II). No data exist regarding the interchangeability of different conjugate vaccine with respect to safety, immunogenicity, or efficacy. However, situations will arise in which the vaccine provider does not know which type of HIB conjugate vaccine the child to be vaccinated had previously received. Under these circumstances, it is prudent for vaccine providers to ensure that, at a minimum, an infant two to six months of age receives a primary series of three doses of conjugate vaccine. These recommendations may change as data become available regarding the

TABLE III. Age-specific Vaccination Schedule for Haemophilus influenzae Type B Conjugate Vaccines Beginning Later Than Two Months

Vaccine	Age at First Dose (Months)	Primary Series	Booster
HbOC (Lederle-Praxis)	2-6	3 doses, 2 mo. apart	15 mo.*
	7-11	2 doses, 2 mo. apart	15 mo.*
	12-14	1 dose	15 mo.*
	15-59	1 dose	—
PRP-OMP (Merck, Sharp, and Dohme)	2-6	2 doses, 2 mo. apart	12 mo.*
	7-11	2 doses, 2 mo. apart	15 mo.*
	12-14	1 dose	—
	15-59	1 dose	—
PRP-D (Connaught)	15-59	1 dose	—

*At least two months after previous dose.

response to different conjugate vaccines in a primary series.

Chemoprophylaxis of household or day-care classroom contacts of children with HIB disease should be directed at both vaccinated and unvaccinated contacts because immune individuals may asymptotically carry and transmit the organism. Because of the time required to generate an immunologic response, vaccination following exposure should not be used to prevent secondary cases. However, the NYSDOH strongly supports extensive use of the HIB vaccine for infants attending day-care facilities; that action should substantially decrease the occurrence of primary cases of HIB disease in day-care facilities. If every child in a household or day-care classroom has been fully vaccinated, chemoprophylaxis is unnecessary.

For more information about the new HIB guidelines, please contact the Immunization Program, New York State Department of Health, Bureau of Communicable Disease Control (518) 473-4437, or one of the following local health department offices:

- Buffalo 716 847-4502
- Syracuse 315 426-7628
- New Rochelle 914 632-4133

- Long Island 516 348-2742
- Rochester 716 423-8094
- New York City 212 285-4610

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Focus on AIDS in New York State

The New York State Department of Health AIDS Institute publishes a newsletter, which discussed various HIV/AIDS-related issues. Each edition focuses on a specific theme and highlights AIDS Institute and state agency initiatives, service delivery profiles, statistics and other pertinent information. Individuals may be added to the mailing list by writing to the New York State Department of Health, AIDS Institute, Bureau of HIV Prevention, Education and Training Section, Corning Tower, Room 729, Empire State Plaza, Albany, NY 12237.

FROM THE LIBRARY

MALPRACTICE INSURANCE

Although many numbers can point to our need for concern, possibly this one statement of fact wraps it up in an unmistakable way: Over the past five years, our closing cost averages, the final settlement amounts of all cases that cost any indemnity at all, have increased an average of 18% per year.

In round dollars, these figures are by years of closure, \$9,100 for 1965, \$12,100 for 1966, \$12,300 for 1967, \$14,800 for 1968, and \$15,600 for the first nine months of 1969. That is \$15,600 in 1969 compared with \$9,100 in 1965. In calculating these averages, we have taken only those cases for which payments have been made, eliminating the no-payment cases.

On the average it takes about five years to settle suits and claims; some settle very quickly; some take fifteen years or more. Of about 4½ million case-closure dollars paid last year, only 14% went to settle 1968 reportings, 11% for 1967 reportings, 15% for 1966, 60% for 1965, and older indexings going back for quite a few years. Here is some of the delay factor which makes it so difficult for insurers to comprehend their underwriting position and to calculate proper rates.

DUNBAR R. UHTHOFF
(*NY State J Med* 1970; 70:1673-1676)

PATHOGENESIS OF FUNCTIONAL BOWEL DISEASE

Edited by William J. Snape, Jr, MD. 389 pp, illustrated. New York, Plenum Medical Book Co, 1989. \$65.00 (hardcover)

This is an excellent book about functional bowel disease. It deals in an up-to-date and comprehensive fashion, with all three aspects indicated in its title: function, bowel, and disease. "Functional" concerns nonstructural abnormalities, including neurological, muscular, endocrine, and psychological problems. "Bowel" concerns the notion that the entire gastrointestinal (GI) tract can be affected, from esophagus to anus, including the biliary tract. "Disease" relates to conceptual and etiologic issues: what separates "normal" from "abnormal," and what the role of disordered physiology is.

The first part of the book is oriented to subjects generic to the irritable bowel syndrome (IBS), psychological aspects, the enteric nervous system, intestinal motility, brain-gut interaction, and dietary influences. The second part focuses on specific organs in the GI tract incorporating and applying the above to areas of the gut.

The authors are experts and the chapters are well organized and thoroughly referenced. Since research in IBS has a relatively recent history, conclusions as to etiology, importance of psychological factors, effect of treatment, and so forth, are appropriately circumspect. For example, the popular notion that natural bran is effective in IBS is subjected to careful scrutiny of the scientific literature with surprising results. In addition, there is a chapter on biliary dyskinesia and sphincter of Oddi dysfunction, a controversial area, where substantive data, much of it by the chapter authors, are discussed with proper distance and perspective.

The question of normal vs abnormal bowel function is addressed in a number of chapters with important emphasis on physician-seeking behavior. Intestinal motility and transit disturbance may affect the esophagus, stomach, small bowel, and colon. This is discussed in terms of physiology and external influences which include diet, medication, and stress.

The treatment of the various symptom complexes is described and evaluated. A number of agents can have a therapeutic role in IBS. With advancing knowledge of altered gut function, this is an area of increasing interest. Prokinetic drugs are an example; they may be useful in esophageal reflux, gastric emptying disorders, and small bowel hypomotility. The limited application of surgery for disease related to IBS, such as severe motility disorders of the small bowel or colon, is discussed in a separate chapter.

The importance of the role of the psyche is mentioned in most chapters, but is fully reviewed by Whitehead, an expert in this area, and also given an excellent historical perspective by Almy, a pioneer in the study of the interaction between stress and the colon.

Colonic dysfunction receives emphasis in a number of chapters in terms of irritable bowel syndrome, chronic constipation, diet, drugs, and normal or abnormal neural and myogenic function.

Overall, this book is a perfect source for anyone interested in the subject of functional bowel disease, including physiologists, psychiatrists, psychologists, and clinicians. It will be of interest to both primary physicians and specialists, since IBS is such a prevalent problem in the general population and a common cause of visits to the physician.

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PRINCIPLES OF AMBULATORY MEDICINE

Third Edition. Edited by L. Randol Barker, MD, John R. Burton, MD, Philip D. Zieve, MD. 1,487 pp, illustrated. Baltimore, Md, Williams & Wilkins, 1991. \$99.00 (hardcover)

As the reviewer of the first two editions of *Principles of Ambulatory Medicine*, it was a pleasure to receive the third edition published in 1991. According to the preface, the third edition has been more efficiently prepared using electronic information management that will allow on-line

access to the text in ambulatory practice settings and continuous updating for future editions. This streamlining has resulted in an edition that is seven pages shorter, 3/4" thinner, 2 lbs 3 oz lighter, and \$16.50 more expensive than the second edition. The type is smaller.

Although the editors and many of the original contributors have remained the same, their overall number has grown to 92, up 14 since the second edition. There are still 14 broad sections categorized by specialty and 102 chapters. Each chapter begins with a short outline of its thematic content with appropriate page assignments. This setup allows the reader to grasp the chapter's structure and access a particular area of interest. As in the previous editions, the signs, symptoms, or management problems of a certain clinical entity constitute the objective of each chapter. Established guidelines and protocols are presented, as are more controversial areas. A clear, succinct understanding of a section may be obtained by reading its chapter independent of the rest of the text.

In spite of the explosive proliferation of medical information in the last four years, the editors have preserved the length of the text while adding an important chapter on the ambulatory care of the HIV patient and expanding the discussion on diabetes mellitus and ambulatory gynecological problems.

Useful graphs, charts, and two-tone illustrations are plentiful throughout the book. The pathophysiology of the various clinical diseases is, for the most part, concisely presented, and diagnosis, treatment, including pharmacology, and preventive measures are adequately explained. Finally, the references are current and of two types, specific and general. The latter are accompanied by a short, useful abstract.

Like the first and second editions, the third suffers from one major oversight. None of the contributors, many of whom are recognized authorities, are family physicians. Although the oversight does not lessen the text's scientific merit, it does reduce its overall credibility when one clearly reads in the first chapter that 31% of all office visits in 1985 were made to

general and family practice physicians, whereas 12% and 11% were respectively made to internists and pediatricians. As a result, the overall impression of this text tends to be adult ambulatory internal medicine. As a suggestion, consideration in future editions should be given to such topics as office surgery, amenorrhea, infertility, and basic pediatrics/adolescent medicine.

The editors continue to maintain a firm, steady hand at the text's tiller. They have skillfully synthesized and presented the latest issues in ambulatory medicine while at the same time reducing text size and length. In spite of its significant cost, *Principles of Ambulatory Medicine* is a worthwhile addition to the library of any physician regularly involved in ambulatory care, although its weight and size prevents easy bedside access. Family practitioners and generalists will need to supplement the book with additional material from obstetrics-gynecology, surgery, and pediatrics texts.

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GOODMAN AND GILMAN'S: THE PHARMACOLOGICAL BASIS OF THERAPEUTICS

Eighth Edition. Edited by Alfred Goodman Gilman, MD, Theodore W. Rall, PhD, Alan S. Nies, MD, and Palmer Taylor, PhD. 1,811 pp, illustrated. Elmsford, NY, Pergamon Press, Inc, 1990. \$79.50 (hardcover)

This book is the eighth edition of the classical pharmacology textbook originally edited 50 years ago by Louis S. Goodman and Alfred Gilman. It appears five years after the preceding edition and fully reflects the information explosion in pharmacology, medicine, and related sciences which has accrued during this time period.

A most impressive change in this edition is the newly organized and authored chapters on adrenergic pharmacology. They provide a comprehensive discussion of the molecular basis of adrenergic receptor action. The concise and accurate diagrams clearly define receptor-induced signal transduction. It is apparent from these chapters that future knowledge concerning receptor structure and function will be of paramount importance for the design of more efficacious drugs for a wide variety of uses. This is

further substantiated by the introduction in another chapter of newly discovered muscarinic receptors and their implication for therapy.

This new edition also has an excellent expanded and revised section on general principles that clearly demonstrates the importance of the intricate relationship between pharmacodynamics and pharmacokinetics. In addition, a new chapter on general principles of toxicology, which includes some basics of emergency medicine, now appears in this section. Also noteworthy in this edition is the extended coverage of antiviral agents, cholesterol lowering drugs, thrombolytic and antiplatelet drugs, gastrointestinal pharmacology, antimicrobial agents, chemotherapy of parasitic infections, antihypertensives, immunosuppressives, antiarrhythmics, benzodiazepines, and dermatologic pharmacology. These chapters provide extensive reviews, which are informative and relevant. The choice of drugs used to illustrate the advances in these rapidly advancing areas is judicious, and the concepts presented in a clear and accurate manner.

A new chapter on hematopoietic growth factors, including erythropoietin and myeloid growth factors, is extremely interesting. It demonstrates the use of recombinant DNA technology for the production of clinically useful drugs that would otherwise be unavailable in sufficient quantities by the usual methods of producing drugs. No doubt, advances in pharmacology and medicine will parallel advances in recombinant DNA technology, and all pharmacology students should be required to be knowledgeable in this area.

The only problems I have with this textbook are the somewhat disappointing chapters on antihypertensive and antineoplastic drugs. Both chapters review the individual drugs without discussing the role and rationale for their use in combination protocols. In addition, the antineoplastic chapter has a weak discussion of drug resistance, a limiting factor for the successful use of these agents. Another criticism I have is with the chapter dealing with oral contraceptives, which I found to be incomplete. It does not discuss the frequency of the side effects of these drugs, nor does it relate the various side effects with the concentration of the estrogenic and progestin components. Another helpful feature would have been a comparison of the efficacy of these drugs with

other commonly used antifertility drugs and methods.

On a personal level, I would have preferred a stronger emphasis on data illustrating the relationship between tobacco and lung cancer in the chapter on drug abuse. I would have also appreciated separate chapters on drug delivery systems, and neonatal and geriatric pharmacology.

Pharmacology encompasses a myriad of diverse topics, and editing a textbook that can also serve as a reference source is a difficult task. This edition of Goodman and Gilman succeeds as an outstanding textbook and as an invaluable reference source. It is authoritative, clear, and modern in concept. It is the most comprehensive textbook of pharmacology available and should be required reading for all students of pharmacology, medicine, and other health-related sciences. Its in-depth extensive reviews also qualify it as a valuable reference source for all medical libraries.

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DERMATOLOGY

First Edition. Edited by Milton Orkin, MD, Howard I. Maibach, MD, and Mark V. Dahl, MD. 677 pp, illustrated. East Norwalk, Ct, Appleton & Lange, 1991. \$37.95 (softcover)

This book is the first edition covering dermatology in the Lange series of affordable books meant for use by medical students, dermatologists, other physicians, and medical personnel. The intention of the authors is to cover most dermatologic subjects, at least to some degree. To trim costs there are no color photographs. The relatively few black and white photos are generally of good quality.

The book has 55 chapters and 45 different authors. There is remarkably little duplication. The consistent style and high quality of writing indicate a strong editorial presence.

Among the outstanding features of this book are the tables and diagrams, which may be better overall than any other current dermatology textbook. Also noteworthy are the unusually clear immunofluorescence photos. There are a few pertinent references

at the end of each chapter, but no footnotes in the text.

The portions of the book of most interest to the practicing dermatologist are the chapters and sections on basic science. For those who studied for board certification 20 years ago, or even ten, the great advances in knowledge of the structure and function of the skin are clearly summarized in about 100 easy-to-read pages.

There is not one poorly written chapter in this book. The outstanding chapters on "Laboratory Evaluation of Immunity" and "Care of Normal Skin, Hair and Nails" merit special praise for conciseness and clarity of writing.

Most dermatologists would not find it difficult to read this book from cover to cover in a few weekends. Other health professionals will find *Dermatology* to be a clear, concise reference book. Dermatology residents will probably find little use for this book considering the lack of comprehensiveness and paucity of references.

Dermatology very admirably accomplishes its purposes. It is highly recommended.

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THE MEDICAL TRIANGLE: PHYSICIANS, POLITICIANS, AND THE PUBLIC

By Eli Ginzberg. 314 pp. Cambridge, Ma, Harvard University Press, 1990. \$27.50 (hardcover)

"The medical profession can no longer count on its erstwhile allies—hospitals, business, insurance companies—to keep the government at arm's length in making decisions that affect health care . . . Physicians are no longer the sole arbiters."

With appropriate attention to the historical, political, and professional aspects, Ginzberg came to the above conclusion in his discussion of the power shifts in American medicine. In the medical triangle in the book's title, physicians seek to provide the most health care for the most money, government aims to limit the money being paid out for health care, and the public looks for the most health care for the least money. Obviously, each side's goals are separate and distinct. There may be resounding conflicts rather than a solid consensus on the major issues.

According to Ginzberg, the following ten principal centers of power influence the structure of the United States health care delivery system: the federal government, state governments, the business community, hospital systems, insurance companies, the legal system, organized consumers, for-profit medical and hospital organizations, the "Guadalajara syndrome" (large numbers of American citizens studying medicine abroad), and the national political arena.

Accepting the power structure concept, the 20 chapters in this book focus on the inevitable tension created in the tug-of-war between maintaining the health care system and the forces aiming to transform the old system. Vital questions include the following: What do we want to change? What do we want to keep? To carry weight and to earn respectability within the councils of the power structure, Ginzberg admonishes that "the medical leadership must not be overly concerned about maintaining the above-average incomes of physicians" Rather, he suggests that American medicine take steps to remain in the medical care forefront throughout the world, assure strong research and development activities, make the system accessible to rich and poor alike, develop efficient and effective operations, and give due respect to the general welfare.

In discussing the changing health care system, Section One notes that between 1910 and the 1970s, the United State health care system was remarkably stable due to the dominance of the medical profession, local sponsorship of hospitals, and the "Robin Hood principle" of subsidization of care for the poor by overcharging the affluent. However, since the passage of Medicare and Medicaid, the system has been increasingly buffeted and battered, resulting in destabilization. Relative to the current emphasis on cost cutting, Ginzberg raises a provocative issue: "The competitive market is an opponent, not an ally, of cost containment." Advertising, marketing, outreach, and expansion lead to duplication of services and over-consumption.

Another section of this book deals with the significant subsystems, such as the academic health centers, the philanthropic foundations, and the community health care centers.

Medical education reforms, the politics of physician supply, and issue of

nursing resources cover the nitty gritty of surpluses and shortages and the impact on the public.

In discussing patients' needs and resources, Ginzberg tackles the major problems of clinical decision making in catastrophic situations, the rationing of care, providing for the elderly, and the medical care for the poor.

Finally, Ginzberg talks about balancing dollars and quality, takes a hard look at cost containment and enumerates the expectations and realities of United States health policy.

All 20 chapters in this book were previously published (between 1985 and 1989) or are in press with the exception of Chapter 5 "High Tech Medicine" and Chapter 18 "Balancing Dollars and Quality." Both the *New England Journal of Medicine* and *Journal of the American Medical Association* have each published three articles; *Health Affairs* published two. Seven other professional journals also published articles. Prior publication does yield some repetition and the feeling that you have read the material somewhere else. Nevertheless, if you have not been exposed to Eli Ginzberg's concepts and comments, *The Medical Triangle* will open up a novel way at looking at the health care delivery system in the United States. No one needs to be told that changes are under way. Ginzberg's book may help readers understand why things are happening and suggests ideas for the future.

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MANUAL OF LABORATORY IMMUNOLOGY

Second Edition. By Linda E. Miller, PhD, Harry R. Ludke, BS, Julia E. Peacock, MS, and Russell H. Tomar, MD. 427 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$39.50 (softcover)

This book is intended for students, faculty of medical technology schools, and practicing laboratory technologists. The authors are experienced in the field of clinical laboratory medicine and are eminently qualified to write this text.

Although there are many books covering general principles and meth-

odologies in immunology, this text differs from the others in the limitation of its scope of discussion to fundamental concepts and by concentrating on technical procedures. The book covers basic principles of immunology, both cellular and humoral, immunomodulators, and immune reactive cells. There is a detailed description of the preparation and handling of specimens and various serological methods. Along with the principles of, for example, lymphocyte quantitation and function, there is a description of the types of lymphocytes and various analytic methods, including flow cytometry. The book also covers the principles and methodologies used for studying immunoglobulins, complement and other serum proteins such as cytokines, acute phase proteins, and others. There is a description of phagocytic activity and the appropriate methods for studying such activity.

The book contains a useful section on the immunologic aspects of important clinical disorders. Viral (cytomegalovirus, Epstein-Barr virus, hepatitis virus, and HIV), fungal (aspergillosis, candidiasis, cryptococcosis), and protozoal infections (toxoplasmosis) are presented in reasonable detail. There is a large chapter on autoimmunity and various disorders related to this phenomenon. HLA antigens and HLA typing methodologies are also presented, but rapid changes in this field make some of the material already outdated. Regarding tumor markers, there are descriptions of principles and methods to determine alpha-fetoprotein, carcinoembryonic antigen, human chorionic gonadotrophin, and lysozyme. Regretably, the discussion has limited use for practicing bedside clinicians, although it is useful for those in clinical pathology.

All the topics in this volume are clearly presented in well-organized chapters, supplemented by useful illustrations and diagrams. The book certainly achieves the authors' objectives and is recommended as a resource for medical technologists, faculty and students of medical technology, and residents in clinical pathology and practicing clinical pathologists.

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TREATMENT PERSPECTIVES IN UROLOGIC ONCOLOGY

Edited by Richard D. Williams, MD,
and Peter R. Carroll, MD. 240 pp,
illustrated. Elmsford, NY, Pergamon
Press, Inc, 1990. \$47.50 (hardcover)

This text is composed of 12 chapters, "focused on several innovative approaches currently in use or under investigation for the treatment of urologic cancer," as stated in the preface. To accomplish this, the editors have amassed an international group of authors, including some of the widely acknowledged experts in their respective fields. This renowned group brings a wealth of experience and expertise to the work. These advantages more than compensate for the inconsistencies in writing style inherent in a book with 29 authors.

The first three chapters deal with renal cancer. Andrew Novick discusses nephron-sparing surgery including rationale, patient selection, and technique. He presents his extensive clinical results to justify his conclusions. Innovative approaches to the systemic treatment of renal cell carcinoma include the use of monoclonal antibodies and of lymphokine-activated killer cells and recombinant interleukin-2. The techniques used in producing these modern weapons, along with a literature review on results of therapy, are also presented. Two well-referenced chapters provide the reader with a basic understanding of the uses, limits, and future directions of these systemic treatments for an otherwise deadly cancer. A general review of biological response modifiers, as they relate to genitourinary cancer, is also outlined.

Fine needle aspirate of the prostate is next discussed. The authors present the techniques and review the cytopathology of prostate aspiration. After an extensive review of the literature, they conclude that "in expert hands" this technique is more sensitive than large-core biopsies. Whether fine needle aspirate will replace large-core biopsy in widespread use remains to be seen. This is especially true with the advent of the automatic biopsy gun, which allows easier and more uniform core biopsies to be taken.

The application of flow cytometry in urologic oncology is still in the developmental stage. Robert Stephenson presents a comprehensive review of the advantages and limitations encoun-

tered with this modality. Flow cytometry has been most widely applied to the study of bladder cancer. Although this technique may provide important information regarding relative risk, its limitations do not allow its substitution in place of classical methods, such as urinary cytology. The combined use of these modalities should result in improved detection rates.

The optimal evaluation and treatment of incidental prostate cancer continues to be debated. The 20 year experience from the University of Iowa is presented, along with comparisons of staging systems and algorithms for management. An authoritative discussion of the pathophysiology and management of the complications of radical prostatectomy is also presented.

Advances in the treatment of stage 1 nonseminomatous germ cell tumors of the testes have markedly progressed over the last 30 years. At present, not only survival but also quality of life are important considerations in choosing the correct method of therapy. Retroperitoneal lymph node dissection (formal versus modified), radiation therapy, and surveillance are discussed with regard to long term survival and potential side effects.

An extensive review of intravesical chemotherapy is presented. Controversies regarding the optimal agent and the frequency and duration of therapy are discussed. Particle radiation is also reviewed. This has had limited application to urologic tumors in the past. The innovative use of high energy charged particles, especially combined with chemotherapeutic agents, may become an important future therapeutic modality as the necessary equipment becomes available.

Howard Scher employs the vast Memorial Sloan-Kettering Cancer Center experience in the treatment of invasive bladder tumors. He presents an extensive review of the literature in order to outline a rational approach to neoadjuvant therapy for this disease in the final chapter.

In spite of being grouped together in a disorganized fashion, the chapters in this text are well researched and amply referenced. The material in each chapter is presented in a clear, concise manner and is generally easy to follow. The authors' own data, along with what has been reported in the literature, are critically reviewed. A strong emphasis is placed on identifying the limitations of each study

before drawing any conclusions from it. The recommendations therefore appear to be realistic and justified on the basis of the data presented. Diagrams are used sparingly but are clear and accurate. Much of the literature review is organized into tables, which are clear and allow easy evaluation.

This text presents the limitations and applications of the more recent techniques in the treatment of urologic oncology. As such, it achieves the goals of its authors, in my opinion.

I would recommend this book to residents in Urology, as well as practicing urologists.

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VASCULAR SURGICAL TECHNIQUES: AN ATLAS

Second Edition. Edited by Roger M. Greenhalgh, MA, MD. 448 pp, illustrated. Philadelphia, Pa, WB Saunders, 1989. \$165.00 (hardcover)

The stated purpose of this book, according to Dr Roger Greenhalgh, the Editor, is to "describe operations which are currently performed by the most eminent vascular surgeons from around the world" and to "update the developments in vascular surgery which have occurred in the five years since the first edition was published." The information is presented in atlas form

with appropriate descriptive material to cover virtually the entire field of vascular surgery, including arterial and venous surgical conditions commonly encountered, as well as newer intra-arterial techniques of transluminal angioplasty and atherectomy. Each of the 56 chapters is authored by a recognized vascular surgeon, these drawn predominantly from Europe, North America, and Australia. As with any multiauthored book, there are inconsistencies in the quality of the illustrations, which are particularly clear in some instances yet difficult to follow in others. Where frequently performed operations such as carotid endarterectomy are described, some attempt is made to present alternative and highly successful techniques. However, the book completely neglects the practice of monitoring tolerance to carotid clamping by EEG monitoring, monitoring the patient under cervical block anesthesia, or simply proceeding without monitoring under general anesthesia, each technique espoused by other eminent vascular surgeons.

Although there are practitioners of endarterectomy for aorto-iliac femoral occlusive lesions, there is no section devoted to this important therapeutic modality, whereas there is much devoted to more recent variations of this approach, balloon catheter dilatation and atherectomy techniques.

The arrangement of this chapter seems logical and comprehensive, with ten divisions, including basic princi-

ples, extracranial arterial surgery, surgery of the aorta, visceral and renal arteries, extra-anatomical techniques, upper limit (incidentally including only techniques for sympathectomy), newer intra-arterial techniques, amputations, portal hypertension, and both varicose veins and deep venous surgery.

In general, the volume succeeds in sketching out surgical approaches to most of the problems encountered in the field of general vascular surgery without becoming involved in major controversies or elaborate explanations. As an example, in an explanation of why Doppler flow assessment is preferred over intraoperative x-ray contrast completion angiography, Dr Greenhalgh states that: "it is less time-consuming and there are no disadvantages!"

This atlas should be of value to medical students and junior surgical residents who require an introduction to a highly complex surgical discipline. It allows them to meet in print a number of well-known vascular surgeons who compress many years and generations of vascular experience into a highly compressed format. There is a minimal and unfortunately inadequate bibliography.

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Tretinoin therapy can produce complete remission in patients with acute promyelocytic leukemia

The goal of the Human Genome Projects, now underway, is to decipher the code for all of the DNA in human chromosomes. A paper by Warrell et al in the *New England Journal of Medicine* (1991; 324:1385-1393), illustrates how such information can be used to understand the pathogenesis of a disease and to begin to develop diagnostic methods and treatments that target the specific etiologic abnormality. By being able to pinpoint the error in the genetic material and having the knowledge of what that region of DNA encodes in a normal cell, the investigators were able, it seems, to induce these undifferentiated leukemic cells to mature, differentiate, and die off, rather than simply destroying them with standard cytotoxic chemotherapeutic agents.

Nine of the 11 patients with acute promyelocytic leukemia described in this report had a translocation of genetic material from chromosome 17 to chromosome 15. DNA sequencing revealed that the region where chromosome 17 breaks off codes for the nuclear retinoic acid receptor- α (RAR- α). Tretinoin (all-*trans*-retinoic acid) was used to treat all 11 patients.

Nine of 11 patients achieved complete remission within a median treatment period of 41 days (range, 24-53 days). The most common adverse effect of tretinoin therapy was headache, which responded to treatment with analgesics; other effects, which were relatively mild, included skin rash, nasal congestion, and hypertriglyceridemia.

"Cell-surface immunophenotyping showed progression from the expression of immature markers on the neoplastic cells at presentation, toward the appearance of mature granulocytic markers during remission." During treatment with tretinoin, there was evidence of "morphologically maturing cells" that carried both immature and mature markers. The authors hypothesize that by flooding the abnormal retinoic acid receptor with large doses of tretinoin; they may have induced a low level of binding sufficient to activate the receptor; modify DNA transcription, and induce the leukemic cells to mature, differentiate, cease replication, and die off, allowing the nonleukemic cells to proliferate. Even after clinical remission, however, aberrant mRNA transcribed from leukemic clones were still evident in some patients.

"Because of the relatively brief clinical experience, the durability of complete remission has not been reliably assessed, nor has the optimal role of tretinoin been clarified," conclude the authors. However, tretinoin yielded low morbidity and should be considered in treating patients with acute promyelocytic leukemia whose disease does not respond to standard therapies.

Psychiatric complaints dominate cocaine-related emergency room visits

Between November 15, 1987 and May 15, 1988, 146 patients presented to the Emergency Department of the Massachusetts General Hospital with cocaine-related symptoms (*Ann Emerg Med* 1991; 20:616-621). Rich and Singer analyzed the characteristics and outcomes of this patient population to determine the most common presenting complaints and whether the method of cocaine use was related to the symptomatology.

The greatest number of patients (30.6%) sought treatment for psychiatric symptoms, followed by neurologic (17.4%), cardiopulmonary (16%), traumatic (11.8%), and addiction-related (11.1%) disorders. Of the 44 patients who presented with psychiatric symptoms, 24 had attempted or had thoughts of suicide; other symptoms included anxiety, acute psychosis, bizarre behavior, depression, and insomnia.

Neurologic disorders included loss of consciousness, seizures, dizziness, confusion, and site-specific loss of feeling. Chest pain was the main cardiopulmonary symptom related to cocaine use. Traumatic injuries generally resulted from motor vehicle accidents, fights, or burns. Addiction-related visits included requests for drug treatment and accidental overdose.

"A notable finding of our study is the strong association between intranasal use of cocaine and cardiopulmonary symptoms. The majority of these patients presented with atypical, nonanginal chest pain and no significant ECG changes."

HIV/AIDS is a growing cause of death among children in the US

"If current trends continue, HIV/AIDS may become one of the top five leading causes of death in this age group [1-4 years] in the next few years." This grim report emanated from the Centers for Disease Control (*Pediatrics* 1991; 87:806-810).

Perinatal infection was the route of HIV transmission for the vast majority (about 94%) of children, aged newborn to four years, who died of AIDS in 1988. Forty-eight percent of children aged 5-14 years who died of AIDS in 1988 were infected perinatally, whereas 26% had had one or more blood transfusions, and 23% had been treated for hemophilia or other coagulation disorders. Improved blood screening and handling techniques should virtually eliminate transmission of HIV via blood or blood products. Counseling and HIV testing for women of childbearing age would then become the predominant means of reducing mother-to-child transmission of HIV and, consequently, of lowering AIDS-related mortality among children.

Analyzing HIV/AIDS mortality among children younger than 15 years by race and region, the authors found that the death rate for black children was nearly six times higher than for whites. Furthermore, the mortality rate in the Northeast was about seven times the rate in the Midwest and the West, with the South

having an intermediate rate. New York, Florida, and New Jersey had the highest HIV/AIDS-related mortality rates among children.

Multiple screening tests improve early prostate cancer detection in initial studies

The American Cancer Society National Prostate Cancer Detection Project began in 1987 as a multicenter study to assess the feasibility of using transrectal ultrasound (TRUS), alone or in combination with other screening tests, to detect the early stages of prostate cancer. A recent paper in the journal *Cancer* (1991; 67: 2949-2958) presents the initial findings of this project,

comparing the effectiveness of TRUS, the digital rectal examination (DRE), and the prostate-specific antigen (PSA) assay.

In studies of 2,425 men aged 55-70 years, the authors found that TRUS is "significantly more sensitive to the presence of cancer than DRE," but is less specific. Positive findings on both the TRUS and DRE yielded the highest positive predictive value (PPV) for cancer. The "PPV for both DRE and TRUS, alone and in combination, were markedly greater when the tests were performed in men with elevated PSA levels. Combined positive TRUS and DRE results in men with elevated PSA levels proved to be cancer in 68% of cases."

FROM THE LIBRARY

CANCER OF THE PROSTATE

Dr. Nathan Jacobson, Syracuse: Cancer of the prostate is a subject which has interested me very much and was the subject of a paper published in the *Annals of Surgery* in 1901. In this paper I reported a case of cancer of the prostate which I had operated in 1898. At that time, I reviewed the literature of the subject. I was able to discover only five cases in American literature of cancer of the prostate at that time. Prostatic surgery had not become popular with American surgeons; but since the prostate has been so freely attacked and removed, we have learned that prostatic cancer is by no means as uncommon as it was supposed to be at that time. We have learned also that cancer of the prostate can occur without making itself manifest. Many times we remove the prostate, thinking it to be simply an enlarged or hypertrophied prostate, when the macroscopic appearance would not justify the conclusion. We likewise find cases of carcinoma of the prostate in which the first symptoms are due to the metastases. This was known as long as 20 years ago. It is known that sarcoma of the prostate can attain an enormous size and appear in childhood and in infancy; that sarcoma of the prostate can also occur in advanced age. Only recently I had occasion to review one of the English medical journals in which I found the report of a case of carcinoma of the prostate. The gland was removed in a man 72 years of age. It weighed 2½ lbs and was of the type of carcinoma that has been described and which fills the entire pelvis. On the other hand, most of our cases of carcinoma of the prostate are of the hard type limited to lobes of the prostate and do not spread beyond it at an early period.

It has been held by some of the French surgeons, and I think justly too, that there is no period at which we can discover the presence clinically of carcinoma of the prostate when the disease has not reached beyond the prostate and has not already involved the lymphatics of the pelvis. The question therefore presents itself, is there any time when one can safely predict that the removal of the prostate gland for carcinoma is to be a radical and a completely successful operation. However, when we are fortunate enough to remove the prostate, presumably for hypertrophy, we may find upon microscopic examination it to be malignant. Carcinoma of the prostate occurs, as a rule, after the 50th year; sarcoma at the 35th year. It seems to me we ought to be very guarded in dealing with a hard nodular prostate, that we may anticipate the condition to be malignant and adjust the surgical procedure accordingly. If it is true, as the English surgeons say, that fully 15 per cent of all cases of prostatic enlargements are carcinomatous, we should be prepared for this condition of things.

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(*NY State J Med* 1912; 12:674-679)

Walter Altbach, MD, Newfane. Died April 2, 1991; age 78. Dr Altbach was a 1936 graduate of the Universitaet Wien, Medizinische Fakultät, Wien, Austria. He was a member of the New York Academy of Medicine, the Medical Society of the County of Niagara, and the Medical Society of the State of New York.

Artandi Tibor, MD, Boynton Beach, Florida. Died April 18, 1991; age 79. Dr Tibor was a 1937 graduate of the Université de Pierre et Marie Curie (Paris VI), U.E.R. Brossais-Hotel-Dieu, Paris, France. He was a Fellow of the American College of Angiology and a Fellow of the American College of Chest Physicians. He was a member of the New York Cardiological Society, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

William H. Berkman, MD, Brooklyn. Died April 23, 1991; age 82. Dr Berkman was a 1936 recipient of the Registrable Qualification Granted by the Scottish Conjoint Board. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Bruce Peter Bernstein, MD, New Rochelle. Died April 30, 1991; age 67. Dr Bernstein was a 1947 graduate of New York University School of Medicine. He was a member of the New York Academy of Medicine, Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Stuart M. Bernstein, MD, Oceanside. Died May 1, 1991; age 57. Dr Bernstein was a 1958 graduate of Baylor College of Medicine, Houston. He was a Diplomate of the American Board of Pediatrics and a Fellow of the American Academy of Pediatrics. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Newton John T. Bigelow, MD, New Hartford. Died January 30, 1991; age 87. Dr Bigelow was a 1928 graduate of The University of Western Ontario, Faculty of Medicine, London, Ontario, Canada. He was a Diplomate of the American Board of Psychiatry and

Neurology and a Fellow of the American Psychiatric Association. He was a member of the Medical Society of the County of Oneida and the Medical Society of the State of New York.

James R. Breed, MD, Poughkeepsie. Died April 18, 1991; age 77. Dr Breed was a 1939 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Surgery and a Fellow of the American College of Surgeons. He was a member of the Dutchess County Medical Society and the Medical Society of the State of New York.

Ralph Matthew Burns, MD, Stowe, Vermont. Died May 1, 1991; age 90. Dr Burns was a 1929 graduate of McGill University, Faculty of Medicine, Montreal, Quebec, Canada. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Elbert Lester Close, MD, Huntington. Died May 21, 1991; age 71. Dr Close was a 1947 graduate of New York Medical College. He was a Diplomate of the American Board of Anesthesiology and a Fellow of the American College of Anesthesiologists. He was a member of the American Society of Anesthesiologists, Inc, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Daniel S. Giddings, MD, Lawrence. Died May 21, 1991; age 74. Dr Giddings was a 1942 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Diplomate of the American Board of Orthopedic Surgery and a Fellow of the American College of Surgeons. His memberships included the American Academy of Orthopaedic Surgeons, the Pan American Medical Association, the American Geriatrics Society, the Nassau County Medical Society, and the Medical Society of the State of New York.

Albert Giordano, MD, Larchmont. Died April 7, 1991; age 87. Dr Giordano was a 1930 graduate of Georgetown University School of Medicine, Washington, DC. He was a member of the Bronx County Medical Society and the

Medical Society of the State of New York.

Markus Hoffman, MD, Monsey. Died March 3, 1991; age 82. Dr Hoffman was a 1935 graduate of the Facoltà di Medicina e Chirurgia, Università di Modena, Modena, Italy. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Victor G. Jimenez-Ponce, MD, New York. Died April 13, 1991; age 54. Dr Jimenez-Ponce was a 1975 graduate of the Universidad Autónoma de Madrid, Facultad de Medicina, Madrid, Spain. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Charles LaVerdi, MD, Bronx. Died March 25, 1991; age 74. Dr LaVerdi was a 1943 graduate of the Middlesex University School of Medicine, Waltham, Massachusetts. He was a Fellow of the American Academy of Family Physicians. He was a member of the American Geriatrics Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

Edith Mead Miller, MD, Poughkeepsie. Died April 18, 1991; age 86. Dr Miller was a 1935 graduate of the University of Rochester School of Medicine and Dentistry. She was a member of the Dutchess County Medical Society and the Medical Society of the State of New York.

Meta F. Mueller, MD, Blauvelt. Died May 1, 1991; age 93. Dr Mueller was a 1924 graduate of the Schlesische-Friedrich-Wilhelms Universität Medizinische Fakultät, Breslau, Germany. Her memberships included the New York Ophthalmology Society, the Pan American Association of Ophthalmology, the American Medical Women's Association, the New York County Medical Society, and the Medical Society of the State of New York.

Hector Perrone, MD, New York. Died May 13, 1991; age 78. Dr Perrone was a 1938 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Diplomate of the American

Board of Internal Medicine and a Fellow of the American College of Physicians. He was a member of the New York Academy of Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

Sol H. Rogatnick, MD, Belle Harbor. Died April 5, 1991; age 63. Dr Rogatnick was a 1954 graduate of the Medizinische Fakultaet, Universitaet Bern, Bern, Switzerland. He was a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Obstetricians and Gynecologist, and a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Walter K. Van Alstyne, MD, Columbus, Ohio. Died May 10, 1991; age 93. Dr

Van Alstyne was a 1926 graduate of Albany Medical College. He was a Diplomate of the American Board of Radiology and a Fellow of the American College of Physicians. His memberships included the New York Academy of Medicine, the Radiological Society of North America, Inc, the Broome County Medical Society, and the Medical Society of the State of New York.

Walter W. Vogt, MD, Sherman, Connecticut. Died April 20, 1991; age 67. Dr Vogt was a 1950 graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio. He was a member of the American Psychiatric Association, the Dutchess County Medical Society, and the Medical Society of the State of New York.

Wolfgang U. Weigert, MD, Poughkeepsie. Died April 27, 1991; age 79. Dr

Weigert was a 1937 graduate of Medizinische Fakultaet, Universitaet Zurich, Zurich, Switzerland. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychiatric Association, the American Geriatrics Society, the Dutchess County Medical Society, and the Medical Society of the State of New York.

Joseph Charles Zumpano, MD, Bronx. Died April 1, 1991; age 84. Dr Zumpano was a 1931 graduate of George Washington University School of Medicine and Health Science, Washington, DC. He was a Fellow of the American College of Angiology. His memberships included the New York Academy of Medicine, the American Geriatrics Society, the Bronx County Medical Society, and the Medical Society of the State of New York.



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The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media, and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1988; 88:456-462). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal's* particular style of publication.

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A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 3,000 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 1,000 and 1,500 words. Other kinds of original essays should not exceed 2,500 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with *Système International* (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

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The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

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References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith² reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear in the text. When there are three or fewer authors, all should be listed; where there are four or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Bowen J: Autoimmune paraneoplastic diseases of the nervous system. *NY State J Med* 1991; 91:2-3.
2. Cotran RS, Kumar V, Robbins SL: *Robbins Pathologic Basis of Disease*, ed 4. Philadelphia, WB Saunders Co, 1989, pp 842-845.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

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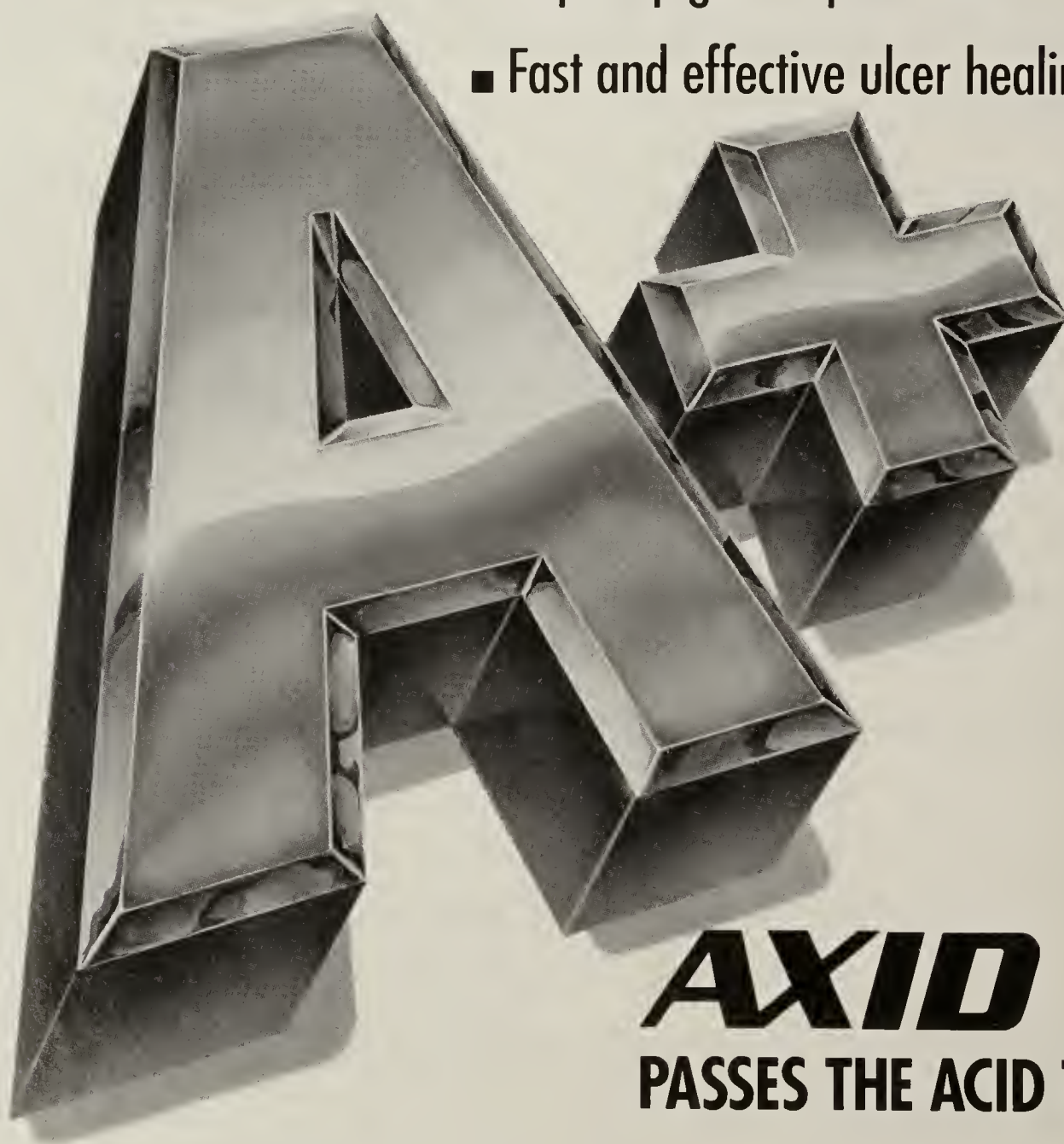
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Precautions: *General*—1 Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.
3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix[®] may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chloridazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H₂-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H₂-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

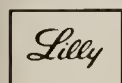
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1. Data on file, Lilly Research Laboratories.
2. *Scand J Gastroenterol* 1987;22(suppl 136):61-70.
3. *Scand J Gastroenterol* 1987;22(suppl 136):47-55.
4. *Am J Gastroenterol* 1989;84:769-774.

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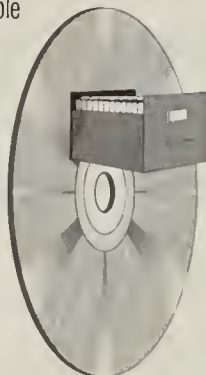
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Easy-to-handle nonadhesive tab

See revised Dosage and Administration section in brief
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nitroglycerin 0.1 mg/hr, 0.2 mg/hr, 0.4 mg/hr, 0.6 mg/hr*



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At the heart of nitrate compliance

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• The only patch with an easy-open tab

Easy to apply —
Easy to remove

Available in four convenient strengths

Patches shown are not actual size.

Transderm-Nitro® nitroglycerin

Transdermal Therapeutic System

Revised Dosage Information

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

This drug product has been conditionally approved by the FDA for the prevention of angina pectoris due to coronary artery disease. Tolerance to the antianginal effects of nitrates (measured by exercise stress testing) has been shown to be a major factor limiting efficacy when transdermal nitrates are used continuously for longer than 12 hours each day. The development of tolerance can be altered (prevented or attenuated) by use of a noncontinuous (intermittent) dosing schedule with a nitrate-free interval of 10-12 hours.

Controlled clinical trial data suggest that the intermittent use of nitrates is associated with decreased exercise tolerance, in comparison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown, but the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered. Further investigations of the tolerance phenomenon and best regimen are ongoing. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS

The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS

General

Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients

Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.



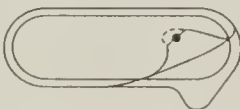
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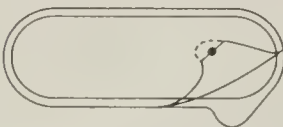
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After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

Drug Interactions

The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have examined the carcinogenic or mutagenic potential of nitroglycerin. Nitroglycerin's effect upon reproductive capacity is similarly unknown.

Pregnancy Category C

Animal reproduction studies have not been conducted with nitroglycerin. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see Overdosage).

Application-site irritation may occur but is rarely severe.

In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Lightheadedness	4%	4%
Hypotension, and/or syncope	0%	4%
Increased angina	2%	2%

OVERDOSAGE

Hemodynamic Effects

The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia

Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b₅ reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq 10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO₂. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

The suggested starting dose is between 0.2 mg/hr* and 0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr* have shown continued effectiveness for 10-12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10-12 hours is sufficient (see INDICATIONS AND USAGE). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours.

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM

A patient leaflet is supplied with each carton.

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0.4 mg/hr	50 mg	20 cm ²	30 Systems...NDC 57267-910-26 **30 Systems...NDC 57267-910-42 ***100 Systems...NDC 57267-910-30
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References:

- Brady EM, Gold OG, Rosenbach HJ. Antianginal efficacy of transdermal nitroglycerin and oral nitrates: The ACTION Study. *Cardiovasc Rev Rep*. October 1988; 40-44.

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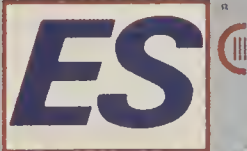
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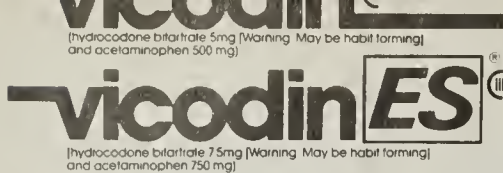
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COMMENTARIES

Surgical complications of HIV infections

The epidemic of human immunodeficiency virus (HIV) infection has affected all of medicine in its myriad complications. The natural history of HIV infection and its common complications are well known to most physicians, but the surgical complications of HIV infection, although well described,^{1,2} are still not widely recognized by most physicians or surgeons.

Surgeons have four common roles in the management of the HIV-infected patient: provision of vascular access, invasive diagnostic procedures, treatment of immune thrombocytopenia, and the management of surgical complications of opportunistic infections or neoplasms.

Most HIV-infected individuals eventually require permanent or semipermanent intravenous access through the use of central venous access of the catheter or implantable port type. Although catheter access is simpler and less expensive, port access is generally preferred for patients' convenience, lack of a transcutaneous device, and lower infection rates.

Invasive diagnostic procedures required in HIV-infected persons include excision of skin lesions, biopsy of peripheral lymph nodes, and occasionally, biopsy of intra-abdominal lymph nodes or masses. Of these, biopsy of lymph nodes is perhaps the most controversial. Lymphadenopathy is not only part of the natural history of HIV infection, but can also be a manifestation of disseminated *Mycobacterium avium* infection, Kaposi's sarcoma, or occasionally, of opportunistic infections. On the basis of unpublished review of our data, we recommend biopsy of peripheral lymph nodes only if the nodes are larger than 2 cm or there are systemic symptoms of opportunistic infection or neoplasm (eg, fever or weight loss) that cannot otherwise be explained. In patients with intra-abdominal or retroperitoneal lymphadenopathy, exploratory laparotomy and biopsy are recommended when there are large nodes (>3 cm), no peripheral adenopathy for biopsy, and systemic symptoms.¹

Immune thrombocytopenia can be a manifestation of HIV infection without other manifestations of AIDS.^{3,4} Often, thrombocytopenia spontaneously resolves. In those patients with prolonged or profound thrombocytopenia, prednisone, danazol, and immunoglobulin infusion have been used, with limited success. Splenectomy is highly efficacious in restoring platelet counts to normal and has minimal morbidity and mortality. We recommend splenectomy for those patients with sustained (>4 months), severe (<25,000 platelets) thrombocytopenia. It has been our casual impression that since the widespread use of AZT, thrombocytopenia has become less common.

Finally, the surgeon can be called on to manage the patients with surgical complications of opportunistic infections or neoplasms.^{5,6} These include gastrointestinal bleeding, intestinal obstruction, or intestinal perforation. The underlying diseases causing these surgical problems include Kaposi's sarcoma, cytomegalovirus ulcers, lymphoma, and all the usual etiologies that are found in the non-HIV-infected patient.

In this issue of the *Journal*, Ravalli et al describe two cases of appendicitis caused by Kaposi's sarcoma.⁷ These cases present well the problems entailed in the care of these patients—a common problem with an obscure cause. As exemplified by these cases, the presentation of surgical complications in HIV-infected persons is similar to that in noninfected persons, although leukocytosis is seldom present in those patients with AIDS and the left shift is not reliably present. Most important, the management of the surgical problem follows standard surgical principles regardless of the stage of HIV infection.

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Boston, MA 02114

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Pulmonary toxicity from amiodarone

Since 1967, amiodarone, a benzofuran derivative, has been widely used in Europe and South America to treat angina, supraventricular and ventricular arrhythmias; it has been used in the United States for the treatment of refractory arrhythmias only since 1980. During this time, amiodarone has been associated with a variety of cardiac and noncardiac side effects, the most serious of which appears to be pulmonary toxicity. There is no direct evidence to link amiodarone to pulmonary injury. However, it has been implicated as a precipitant of pulmonary toxicity in the cases reported because no other reason could be found for the lung injury, radiologic lesions cleared when amiodarone was discontinued, lung biopsies revealed changes similar to those seen in other drug reactions and/or specific therapy for other possible pulmonary disorders failed to reverse the process.

Since the first report of amiodarone-associated pulmonary toxicity in 1980,¹ there have been numerous reports of pulmonary damage secondary to the drug. The clinical features of pulmonary disease occurring in association with amiodarone treatment include symptoms occurring after five to six months of therapy,² whose onset is generally subacute with dyspnea on exertion, a nonproductive cough, fever, malaise, and weight loss usually progressing over a two to three month period. In addition, pulmonary toxicity is rare in patients receiving 400 mg or less of amiodarone daily. The report of Rubin et al, in this issue of the *Journal*, differs from the classic description of pulmonary amiodarone toxicity in a number of ways: symptoms of pulmonary toxicity occurred within six weeks of initiation of therapy, pulmonary symptoms were acute in onset rather than subacute or chronic, and when clinical toxicity occurred daily doses of the drug were only 400 mg.³ As with other pulmonary toxic drugs, amiodarone may have a larger spectrum of clinical toxicity than is presently appreciated. The lung has a number of homeostatic mechanisms for maintaining a fine balance between damaging reactions and protective detoxification pathways. Several of these systems may be affected by exogenous agents and depending on which system of lung injury is activated, the clinical signs, symptoms, course, and prognosis of drug toxicity may vary accordingly. For example, drugs may include pulmonary damage by triggering the formation of reactive oxygen metabolites which can cause direct toxicity or release immunoreactive substances that produce secondary inflammatory reactions within the lung. The former may

produce a more protracted clinical course, whereas the latter may cause acute onset of symptoms. Additionally, drugs can affect local lung immune mechanisms, which may be reversible, or may upset the balance between collagenesis and collagenolysis and/or the protease and antiprotease systems, which might cause irreversible damage.

Although the mechanisms of lung injury by amiodarone are unknown, it is thought that the drug is toxic to the lung at least in part, by impairing normal phospholipid catabolism by phospholipase through binding to lysosomal lipids.⁴ This in turn causes the accumulation of phospholipid within lysosomes resulting in lung damage. Reversibility of these abnormalities may be related to the dissociation rate of the drug from phospholipid binding sites. Hence, the variability in the relationship of pulmonary toxicity to amiodarone dosage could be related to the variation in this dissociation rate.⁵ Although phospholipid accumulation within lung cells might account for direct pulmonary damage, other indirect modes of injury may also take place widening both the pathogenetic and clinical spectrum of lung injury from amiodarone. Rubin et al and other investigators^{3,6,7} have postulated an immunologic mechanism of amiodarone-induced pulmonary toxicity on the basis of the finding of an increase in the percentage of bronchoalveolar lavage lymphocytes and inversion of the normal helper-to-suppressor ratio in patients with clinical pulmonary toxicity. In a paper by Akoun et al,⁶ in vitro studies of a patient's leukocytes suggested hypersensitivity to amiodarone, including lymphocyte transformation and basophil degranulation in the presence of the drug. Although the relevance of the above findings to clinical amiodarone pulmonary toxicity remains unclear, the cause of lung injury by amiodarone most likely is multifactorial.

Of further interest is the 50% neutrophils found in the lavage of the first patient described by Rubin et al.³ Bronchoalveolar lavage (BAL) neutrophilia has been implicated in some forms of acute lung injury, and increased numbers have been found in BAL fluid of some patients with bleomycin toxicity⁸ and the adult respiratory distress syndrome (ARDS).⁹ Other studies have demonstrated that greater numbers of neutrophils in the lower respiratory tract of patients with *Pneumocystis carinii* pneumonia¹⁰ and idiopathic pulmonary fibrosis¹¹ are associated with a poorer patient prognosis. These data raise several important questions: what was

the role of the neutrophils in this patient, did they produce lung injury, was the increase in the number of neutrophils directly caused by amiodarone or was it the result of ARDS, and does the presence of neutrophils portend a worse prognosis in patients with amiodarone toxicity. The paper by Rubin et al not only describes another facet of clinical amiodarone pulmonary toxicity, but also raises many issues about its mechanisms of lung injury and provides a stimulus for further research to answer these queries.

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FROM THE LIBRARY

INTERRELATIONSHIPS BETWEEN THE FINANCING OF CARE AND THE DELIVERY OF SERVICES

Acute care for AIDS patients has fallen disproportionately on public and church institutions in inner-city areas of northern New Jersey. This phenomenon has been referred to as the "ghettoization of PWAs." Green has indicated that by 1991, 2% of all medical/surgical beds will be occupied by AIDS patients. In New Jersey, the rate at one institution is currently at 50%. Five hospitals have cared for more than 100 AIDS patients, six hospitals have cared for 50-100 patients, 15 hospitals have cared for 25-50 patients, and most other hospitals have cared for at least one patient. Much of this trend is due to the demographics of the disease; however, to some extent we are aware of the inappropriate referrals of PWAs. Patient referral may sometimes be due to the "inability to provide appropriate care." Inappropriate referrals which essentially deny access to care, and are the result of HIV routine testing without informed consent or suspicion of positivity, are clearly unethical and intolerable.

High caseloads—ones that are rapidly increasing—cause concern about the operational aspects of hospitals. Similar concerns exist in other community-based health care agencies. There are staffing concerns; institutions have recognized the difficulty in recruiting teams of professionals necessary to work with PWAs. Ongoing training and support systems are necessary. The development of multidisciplinary care teams for PWAs is one of the greatest challenges facing the health care system.

Communities in New Jersey have accepted the fact that PWAs are treated in hospitals. But what about the future? As caseloads increase disproportionately in some hospitals, they may lose other patients who have freedom of choice and choose not to be treated in an "AIDS hospital."

STEVEN R. YOUNG, MSPH
NY State J Med 1988; 88:258-262

Physicians' attitudes toward the autopsy of patients with AIDS

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ABSTRACT. In spite of the value of autopsy in modern medicine, autopsy rates continue to decline. This decline has been especially pronounced for patients who die of acquired immunodeficiency syndrome (AIDS). In this paper, we assess the attitudes of house officers toward the autopsy in AIDS patients. The survey encompassed 112 internal medicine housestaff (IMHS) and 37 pathology housestaff (PHS) at two New York City university hospitals that care for large numbers of AIDS patients. A self-administered questionnaire rated attitudes and practices concerning the autopsy in AIDS patients.

Of IMHS, 83%, and of PHS, 89% answered the questionnaire. The vast majority of IMHS felt that the autopsy rate in persons dying of AIDS was too low; only 39% of PHS shared their view. Of the PHS, 36% felt the rate was too high and should be decreased. These PHS felt the autopsy rarely resulted in useful information and unnecessarily exposed the pathologist to human immunodeficiency virus (HIV) infection. The IMHS wanted more formal training in methods of discussing these issues with the patient and family. We conclude that there is a need for postgraduate teaching programs to educate on issues concerning the autopsy. Specifically, the IMHS need instruction on communicating with the family about the autopsy, and the PHS need instruction on the risks of acquiring AIDS from occupational exposure.

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Although there have been many advances in diagnostic technology over the past 20 years, the usefulness of the autopsy has not declined.¹ A considerable body of literature exists substantiating the varied benefits of the autopsy.² These include assessing the appropriateness of clinical care, verifying the accuracy and completeness of clinical diagnoses, aiding in the discovery of previously unrecognized diseases, providing reassurance or new information to family members, investigating the effects

of new drugs, playing a vital role in medical education, assisting in medicolegal investigations, and producing epidemiologic information. In spite of these benefits, there has been a pronounced decline in autopsy rates over the past 40 years.³ Moreover, patients who fall into certain demographic groups or die of certain diseases, such as the AIDS, are less likely than others to receive an autopsy.

AIDS is a major cause of death in many hospitals in the United States. Several studies have suggested that medical conditions, unrecognized during the patient's life, are frequently discovered at autopsy, particularly when the cause of death is infectious in nature.⁶ This has certainly been the case with AIDS; a substantial amount of what we have learned about the pathophysiology of AIDS and HIV infection has come from the autopsy.⁷ In spite of this, autopsy rates have continued to decline. For example, since the initial reports of AIDS in 1981, the autopsy rate among patients dying of AIDS in New York City has dropped from 46% to 17%.⁸

The decision to perform an autopsy may involve input from several sources including the patient, the family, the primary care giver, and the pathologist. This study focuses only on the role of the physician. During our years as housestaff, we found it particularly difficult to deal with issues relating to the autopsy in persons dying of AIDS. Given these observations, we conducted a study to assess the attitudes and practices of physicians-in-training toward the value and use of the autopsy in people dying of AIDS.

PATIENTS AND METHODS

A multiple choice questionnaire was developed to obtain information from housestaff concerning their use of the autopsy. All questions were closed ended and designed to address general beliefs about the autopsy, beliefs about the autopsy in people dying of AIDS, the frequency with which autopsies are requested and completed, and reasons for requesting or not requesting autopsies. The questionnaire was pilot tested in a group of 20 residents to evaluate its clarity. The results from the pilot questionnaires were excluded from the final data analysis.

Our study sample of house officers came from the Departments of Medicine and Pathology of two New York City university teaching hospitals (one private and one public) that cared for a large number of patients with AIDS. During June 1987, the self-administered survey was delivered to the hospital mail boxes of all first- and second-year internal medicine residents and pathology residents from all years. Third-year IMHS were ex-

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cluded because a majority were on elective rotations and thus were unavailable for study.

A detachable cover sheet, with an identifying number, explained the study and assured confidentiality. The investigators used this identification number to follow up on nonrespondents using written and telephone reminders, and when the questionnaire was returned, they destroyed the cover sheet to ensure respondent anonymity.

Survey Measures. Respondents were asked to answer 97 questions: multiple choice (10), Likert format (82), and true/false statements (5). Descriptive questions dealt with demographics and experience with autopsies and with persons dying of AIDS. Questions using Likert scales dealt with reasons for obtaining an autopsy, beliefs about the value of autopsy, and attitudes toward the declining autopsy rate. The IHMS also responded to questions concerning their beliefs and personal experience in requesting permission for an autopsy and about the autopsy's educational value. Pathologists answered questions concerning their perceived risk of infection from performing autopsies.

RESULTS

Eighty-three percent of the 112 IHMS and 89% of the 37 PHS completed and returned the questionnaire. Demographic characteristics of both groups are presented in Table I.

During the six months prior to the administration of the questionnaire, 77% of the IMHS had cared for at least 20 persons with AIDS, and no one had cared for fewer than five persons with AIDS. In addition during this same period, 46% of the PHS had studied specimens of at least 20 persons with AIDS.

Thirty-four percent of the IMHS stated that none of the patients they cared for who died of AIDS received an autopsy. Eighty-three percent of the time that an autopsy was requested, it was the intern who obtained permission from the family. In patients dying of diseases other than AIDS, interns requested permission from the family 74% of the time.

According to IMHS, families of patients dying of AIDS refused permission for an autopsy more than 50% of the time compared with 27% of the time for patients who die of other diseases. Some IMHS reported that they found it emotionally more difficult to request permission for an autopsy when a patient's death was caused by AIDS (Table II).

The majority (72%) of the IMHS thought that the autopsy rate needed to be increased for all groups (patients with AIDS as well as those dying of other diseases). Eighty-seven percent of IMHS

TABLE II. Attitudes Concerning Autopsies and AIDS Patients

Percentage of Respondents Who Agreed With the Following Statements	Medicine (%) (n = 93)	Pathology (%) (n = 33)
It is more difficult for me to discuss an autopsy with the family of a patient with AIDS than with the family of a patient dying of other illnesses	11	—
It is more stressful for me to perform an autopsy on a patient with AIDS than on other types of patients	—	79
Pathologists are overly concerned with contracting the AIDS virus	23	6
Pathologists should be able to choose not to perform an autopsy on a patient with AIDS if they wish	37	36
In AIDS, we are able to obtain relevant information from antemortem testing, making the autopsy unnecessary	9	18
The families of patients with AIDS are under such emotional stress that it is inappropriate to discuss an autopsy	5	3

believed that the current autopsy rate for patients dying of AIDS was too low. Eighty-five percent thought the rate was too low for patients dying of other diseases. None of the IMHS thought that the autopsy rate was too high or that it should be decreased.

This contrasts with the PHS: only 39% thought the AIDS autopsy rate was too low and needed to be increased. Conversely, 36% of PHS thought that the rate was too high and needed to be reduced. Many pathologists (42%) believed that hospitals should be required to perform autopsies on a certain fixed percentage of hospital deaths; however, only 15% of the pathologists sampled thought that persons dying of AIDS should be included in this requirement.

More than three quarters (79%) of the PHS believed that performing autopsies on AIDS patients was more stressful than performing autopsies on patients who die of other diseases. Seventy-three percent of pathologists agreed with the statement that while performing an AIDS autopsy: "I am regularly concerned about the risk to my health." In addition, 49% of the PHS and 25% of the IMHS thought that pathologists are at higher risk of acquiring AIDS from their work than are other physicians.

The reason most commonly cited by the IMHS for low AIDS autopsy rates was "reluctance on the part of families to grant permission for the autopsy" (Table III). On the other hand, pathologists most frequently cited the "reluctance of clinicians to obtain permission" as a major reason for the low autopsy rate. Yet, nearly all (95%) the IMHS felt comfortable asking permission to perform an autopsy. Although the IMHS stated that families often refuse to discuss autopsies, 94% thought that requesting permission for an autopsy does not damage the clinician's rapport with the deceased's family.

Sixty-six percent of the IMHS had been formally taught about the value of an autopsy. Yet, only 40% of the IMHS recalled ever having received instruction on how to request an autopsy, and 78% thought they needed more instruction in methods for obtaining permission for an autopsy.

TABLE I. Characteristics of Internal Medicine and Pathology Residents Surveyed

Characteristic	Medicine (%) (n = 93)	Pathology (%) (n = 33)
Private hospital	53	33
Public hospital	47	67
Year of training		
First year	31	21
Second year	65	24
Third year	0	15
Other year	3	39
Female	37	30
Religion		
Catholic	18	24
Jewish	48	38
Protestant	15	17
Other	19	17
AIDS experience in past six months		
Cared for greater than 20 patients with AIDS	77	46
Cared for less than five patients with AIDS	0	30

TABLE III. Reasons Given for Low Autopsy Rates

Type of Patient	Medicine (%) (n = 93)		Pathology (%) (n = 33)	
	AIDS	Other	AIDS	Other
Reluctance of housestaff to request autopsies	61	39	39	58
Reluctance of attendings to encourage housestaff to request autopsies	84	39	36	58
Reluctance of families to grant permission for autopsies	94	62	39	32
Reluctance of pathologists to perform autopsies	—	1	18	6
Ignorance of housestaff about the importance of autopsies	18	9	52	24

DISCUSSION.

The autopsy remains an underused procedure for quality assurance, medical education, and epidemiology.¹ In a general population, 24% of systemic infections diagnosed at autopsy had been missed in the clinical findings.⁴ Unrecognized findings may be even more important when a patient dies of AIDS, a disease for which the pathophysiology and epidemiology are still under active investigation. In one study, 74% of patients dying of AIDS had treatable diseases found during autopsy that were not suspected clinically.⁹

The failure to use autopsies more fully in patients with AIDS seems to be explained in part by a fear of contagion among pathologists. In this study, 73% of the pathology house officers expressed concern for their health when performing autopsies on patients with AIDS. Furthermore, one third of all pathology housestaff polled thought that pathologists should be able to choose whether or not to perform an autopsy on a person who dies of AIDS. This sentiment has been echoed by some leading pathologists who have publicly refused to provide services to persons infected with HIV. Concern about acquiring AIDS through caring for patients with the disease is not limited to pathologists. For example, one study and several other reports have demonstrated that many primary care physicians are reluctant to care for persons with AIDS because of a fear of contagion.^{10,11}

Medical educators at all levels are concerned with these attitudes. Health care professionals' attitudes toward HIV not only affect patient care, but also training programs. For example, residency directors in all specialties from urban centers with sizable HIV-infected populations report large drops in the number of applications. Likewise, concern about caring for patients with AIDS is one factor that may influence medical students' career choices. Several studies have documented that fears and perceptions of patients with AIDS begin early in training.¹²⁻¹⁵ It is therefore imperative that these concerns be discussed at the earliest possible period in a health professionals' training. By waiting until the residency years, educators miss the window during which many attitudes and beliefs are formulated.

Discrimination toward patients with AIDS is not limited to health professionals. Funeral home operators and morticians also refuse to provide service to those dying of AIDS.¹⁶ This sort of discrimination has led many physicians to take drastic steps to protect the confidentiality of their patients with AIDS. For example, in this study, more than 40% of the IMHS agreed with the statement: "On occasion I have put down a false diagnosis on a patient's death certificate in order to protect either the family or the patient." Practices such as these raise serious problems for health officials, researchers, and others who rely on death certificates for accurate epidemiologic data. It will be difficult to counter these attitudes as long as physicians continue to fear discrimination against patients dying of AIDS and their families.

In spite of the perceived risk of infection to health care providers, epidemiologic studies suggest only a small occupational risk of infection associated with caring for persons with AIDS.¹⁷ It may be possible to allay the fears and misperceptions of house officers through educational programs dealing with procedural safety and risk evaluation.

Both groups of house officers recognized the important role of the family in gaining consent for the autopsy. Given the protracted course of the illness experienced by people with AIDS, it is understandable that at the time of death some families may wish to disallow all further invasive procedures. Other families may simply be expressing the wishes of the deceased. However, it may be that family members are not routinely told of the many benefits offered by the autopsy. On the other hand, refusal may be because of the manner in which permission from the family is sought. This time-consuming and emotionally difficult task often falls to the intern, the least experienced and most overworked member of the health care team. Permission for an autopsy may be more successfully sought by the more experienced attending physician or senior resident. It is clear that the house officers surveyed thought there was a need for more formal training in discussing the autopsy with the patient or family. Ideally, this instruction should be provided early in the training program. This survey did not attempt to examine why families refuse to grant permission for an autopsy, although this would be an important investigation.

Currently, there is reason to be concerned that persons dying of AIDS may not be getting the care they deserve. Ratzan and Schneiderman¹⁸ suggest that: "By pulling away from the patient at death, without trying to complete the continuum of medical care through the autopsy (if the autopsy is clinically indicated) . . . is to abandon the patient." The medical profession has a responsibility to ensure that the autopsy is used in patient care, including the care of patients dying of AIDS.

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Characteristics of HIV-infected adults in acute care hospitals in New York State, 1984-1986

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ABSTRACT. The New York State acute care, hospital discharge database was used to create a longitudinal case history file for all adult inpatients infected with the human immunodeficiency virus (HIV). From 1984 through 1986, 12,958 individuals with HIV-related diseases were treated in acute care hospitals throughout the state. Approximately 80% of those people resided in New York City, and nearly half of them were between ages 30 and 39 years.

Over the three-year period, the proportion of females increased from 11.8% to 16.6%. The per diem charge increased slightly, although the total length of stay for the first year of HIV illness declined sufficiently to decrease the total charge for the year. Examination of the pattern of inpatient stays and intercurrent days shows the first and last hospital stays to be longer than those in between, although the days between stays decreased as the number of admissions increased. The hospital stay in which a patient died was typically of longer duration than earlier stays. The average charge for HIV-related hospital care among inpatients during their first year of illness was approximately \$20,000.

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New York City and San Francisco accounted for the majority of acquired immunodeficiency syndrome (AIDS) cases during the early years of the epidemic, but today all states have reported cases. New York State and California account for 22.3% and 19.5%, respectively, of the nationally reported cumulative incidence. Through November 1990, the Centers for Disease Control (CDC) has received 152,634 AIDS case reports from all states.¹

Given the large and growing number of individuals infected with HIV, analysis of the amount of acute care

resources used by those individuals can provide an important baseline for comparison with future demands on the system. A number of authors have attempted to answer these questions. The first cost analysis and projection was done by Hardy et al² in 1986. Andrulis et al analyzed data from 1985³ and 1987⁴ from a national sample of hospitals. The 1985 study showed that patients with AIDS spent an average of 32 days per year as inpatients, with 1.6 admissions per patient per year and an average length of stay of 19 days. By 1987, the average number of inpatient days per year dropped to 26, the average number of per patient admissions per year remained at 1.6, and the average length of stay dropped to 17 days. Other investigators have also reviewed costs, charges, and frequency of admission patterns: Berger⁵ studied 26 cases in Maryland; Seage et al⁶ assessed 45 patients in Massachusetts; Scitovsky et al⁷ reported on 445 patients treated at one hospital in San Francisco; Thomas and Fox⁸ conducted a study of four hospitals in the New York City metropolitan area; and Lafferty et al⁹ analyzed inpatient utilization for 165 patients with AIDS in Washington State. Each of these investigations has added to the knowledge of hospital utilization, either on the basis of a sample of patients from a large population or the universe of patients from a somewhat closed population.

The purpose of this report is to describe the hospital usage of all adult patients with a diagnosis of AIDS or HIV infection in New York State during the period 1984-1986. More than 20,000 discrete hospital discharges were linked (via computer) to form individual case records, yielding one of the largest AIDS/HIV acute care utilization databases available to date. A thorough examination of information available from this data set will provide a detailed baseline against which

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TABLE I. HIV Diagnoses and ICD-9-CM Codes

ICD-9-CM Code	Description	Initiated
042.x	Includes AIDS	Fall 1986
043.x	Includes AIDS-related complex (ARC)	Fall 1986
044.x	Includes other HIV infection	Fall 1986
795.8	Positive serological or viral culture for HIV	Fall 1986
279.19	Other deficiency of cell-mediated immunity as a principal or secondary diagnosis	Fall 1982
279.10	Immunodeficiency with predominant T-cell defect as a principal or secondary diagnosis	Fall 1982
279.3	Unspecified immunity deficiency as a principal diagnosis with or without 279.10 or 279.19 as a secondary diagnosis	Fall 1982
136.3	Pneumocystosis as a principal diagnosis with or without 279.10 or 279.19 as a secondary diagnosis	Fall 1982

future changes in HIV/AIDS patterns of care can be assessed.

PATIENTS AND METHODS

The New York State Department of Health maintains the Statewide Planning and Research Cooperative System, which collects a discharge data abstract for every New York State acute care hospital stay (excluding psychiatric and federal facilities). Billing data are subsequently linked to the discharge record, producing an expanded record containing demographic, diagnostic, utilization, and fiscal information. A linkage method was created and validated that assembled the separate records into patient-specific case histories, identified as the HIV Longitudinal File (HIVLF).¹⁰ Only those patient's discharges listing ICD-9-CM codes indicative of HIV or AIDS (Table I) were included in the linking process. The HIVLF encompasses the period of January 1, 1983 through October 1, 1987. The HIVLF was developed

completely from existing data files already used by the Department of Health for other purposes.

The longitudinal file has certain limitations. Explicit patient identifiers are not available on the source file, so a number of variables (ie, date of birth, sex, address, health insurance policy number) must be used to identify a given patient across multiple admissions. Inherent in this methodology is the risk of errors in the completeness of cases. Kaufman et al¹⁰ have estimated the case completeness rate at 88%, with an overestimation of cases due to failures in record linkage at 10%.

Cases were grouped into cohorts on the basis of the date of their first HIV-related acute care admission. Cohorts were created in six-month intervals to ensure adequate numbers for examination of trends and for consistence with published state AIDS surveillance reports. To be included in this analysis as a "first HIV-identified stay," there had to be at least one year during which HIV was not reported prior to an HIV-identified stay. Since hospitals did not identify HIV-infected patients prior to the fall of 1982, sufficient time is not available until late 1983 to have a 12-month period without HIV identification. Therefore, only patients admitted to a hospital since January 1984 without evidence of an HIV-related stay in the previous 12 months were accepted into the study.

During the early years of the HIV/AIDS epidemic, explicit ICD-9-CM codes were unavailable. The 1986 revision of the ICD-9-CM provided codes 042-044 and 795.8 for this purpose. The discharge diagnoses for the 1982-1986 cases in our file were compared against the 1986 coding instructions, and codes in the 042-044 range were assigned retrospectively.

Demographic, geographic, and diagnostic data are presented for the six cohorts of adults (> 12 years of age) between 1984 and 1986. The principal and four secondary diagnostic codes for each discharge were examined for the presence of codes indicating the presence of *Pneumocystis carinii* pneumonia (PCP) or Kaposi's sarcoma (KS). Patient records with either of these codes were flagged for subsequent analysis; records with diagnoses other than PCP or KS were coded "other." Patterns of hospital use by vital status are reviewed in terms of the number of admissions and intercurrent days (ie, number of days between hospital admissions) for the first 12 months subsequent to the initial HIV-

TABLE II. Age, Sex, and Residence Characteristics of Individuals, 13 Years and Older, When First Hospitalized With an HIV-related Condition

	Date of First HIV-related Admission					
	1984		1985		1986	
	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec
Number of cases (%)	977	1,342	1,791	2,349	2,925	3,574
Gender						
Male	88.0	87.9	85.1	85.4	84.6	83.3
Female	11.8	12.1	14.5	14.5	15.3	16.6
Unknown	0.2	0.0	0.4	0.0	0.1	0.1
Residence						
New York City	80.9	82.2	81.1	81.1	79.8	79.0
Rest of state	15.3	15.4	15.3	15.9	16.4	16.9
Out of state	3.9	2.5	3.6	3.0	3.8	4.1
Age						
13 to 19 yr	0.9	0.8	0.6	0.5	0.5	0.7
20 to 29 yr	21.2	21.1	19.7	20.5	19.4	19.4
30 to 39 yr	45.9	44.9	48.6	47.4	49.7	50.3
40 to 49 yr	21.1	21.3	21.5	22.3	20.9	19.8
50+ yr	11.0	11.9	9.7	9.3	9.5	9.9
First diagnosis*						
KS + PCP	3.5	4.5	3.6	2.9	2.5	1.8
PCP	45.9	44.6	45.6	42.8	40.2	37.2
KS	8.4	8.8	7.9	6.0	4.9	4.8
Other	42.3	42.0	42.9	48.3	52.3	56.3

*KS = Kaposi's sarcoma; PCP = *Pneumocystis carinii* pneumonia.

TABLE III. Number of Stays, Mean Length of Stay, and Mean Time Between Stays for Cases Diagnosed in 1984 and 1985

Number of Admissions Within One Year	Number of Cases	Length of Stay (Days) and Admission Number						Mean Total Days
		1	2	3	4	5	6	
1	3,872	28*						28
2	1,219	25 (114) [†]	25					50
3	645	25 (94)	17 (69)	26				73
4	362	22 (81)	15 (55)	15 (49)	22			72
5	160	21 (70)	15 (53)	14 (43)	13 (34)	20		80
6+	201	21 (52)	15 (34)	13 (29)	10 (29)	10 (27)	13	98
Total	6,459							

*Average number of days per stay.

[†]Days between stays are provided in parentheses.

identified admission for the 1984 and 1985 cohorts. Although records were available through 1986, the analysis ended with the 1985 cohort to allow 12 full months of follow-up for cases first admitted in December 1985. All analyses presented here will focus on the 12-month period subsequent to the first HIV-identified admission to permit accurate comparisons among the cohorts. Changes in utilization for length of stay, charges per diem, and total charges during the first year after HIV identification are presented for the first cohort of 1984 and the last cohort of 1985 to permit identification of changes over time. For stays straddling the one-year time period, the days and charges were allocated to the first year on the basis of the fraction of the stay occurring in that year. Utilization data for the four cohorts of 1984 and 1985 were analyzed for trends.

RESULTS

During the period 1984–1986, there were 12,958 individuals hospitalized in New York State with AIDS- and HIV-related infections. Detailed data on the composition of the six-month cohorts are presented in Table II. The number of new HIV-related patients from the first to the last cohorts increased by a factor of 3.6, and state AIDS surveillance figures show an increase of CDC defined AIDS cases by a factor of 2.8.¹¹ The geographic distribution between New York City and the rest of the state remained relatively stable, with approximately 80% of the cases residing in New York City. The proportion of women steadily increased from 11.8% to 16.6% of all cases. The proportion of individuals aged 30–39 increased by nearly 5% and was drawn equally from those in the adjacent older and younger decades of life. The proportion of whites decreased by 8%. In terms of diagnoses at first admission, the proportion of “other” diagnoses increased whereas PCP and KS declined, both alone and in combination.

Diagnostic data for first admission of patients in 1984 and 1985 were coded in accordance with the ICD-9-CM criteria in the 1986 revision. The proportion of first admissions coded to 042.x varied between 80.8% and 82.8% with no clear trend over time. The remainder of cases were coded to 043.x, 044.x, and 795.8.

Table III presents the patterns of hospitalization for individuals first admitted for an HIV-related infection in 1984 or 1985. Each case presented in the table was followed for 12 months from the date of the first HIV-related admission. Nearly 60% of the cases presented in the table were hospitalized only one time. The remaining patients were hospitalized between two and 26 times, with only 1.7% hospitalized more than six times. The pattern of days per admission is “U” shaped, with the first and last stays being longer than the intermediate stays. The number of days between admissions shows a consistent pattern, decreasing with each subsequent admission. The mean total length of stay for all four cohorts was 42 days (SD = 43 days).

Table IV presents utilization experience for those who died in the hospital. More than 42% of the patients died in the hospital within 12 months of their first admission. The vital status of the remainder is not known; we only know that they did not die in the hospital. Comparison of those who died versus those who survived by number of admissions shows that the stay in which a death occurred was significantly longer than stays for the survivors at each number of admissions. (Wilcoxin, $p < .01$, for first through fifth admission.) In addition, the days between stays are generally shorter for those who died in the hospital than for those who did not. For patients with the same number of records per case, the last stay for those who died was longer than for those who survived the same number of admissions. Table V presents utilization and charge data by cohort for hospitals throughout the state, excluding flat-rate hospitals. (Note: Flat-rate hospitals use an all inclusive rate structure that does not reflect charges as a function of services used. During the study period, 25 hospitals were classified as “flat rate,” with 13 operated by Health and Hospitals Corporation in New York City. Exclusion of these facilities should more accurately reflect charges as a function of services used.) Of the 6,459 cases, 4,481 (69.4%) had complete billing information; among the 4,481 cases, 1,551 (34.6%) were excluded from the analysis because they used only flat-rate facilities or a combination of flat- and variable-rate hospitals. These reductions leave 2,930 cases or

TABLE IV. Cases First Admitted in 1984 or 1985 Who Died in the Hospital

Number of Admissions Within One Year	Number of Cases	Length of Stay (Days) and Admission Number						Mean Total Days
		1	2	3	4	5	6	
1	1,576	33*						33
2	529	27 (89) [†]	32					59
3	324	26 (75)	19 (54)	28				73
4	177	22 (71)	17 (48)	16 (41)	23			79
5	66	20 (53)	15 (49)	14 (39)	15 (30)	25		89
6+	85	23 (52)	15 (26)	14 (24)	11 (26)	9 (21)	15	103
Total	2,757							

*Average number of days per stay.

[†]Days between stays are provided in parentheses.

TABLE V. Number of Admissions (Admits), Charges, and Length of Stay by Cohort* in 1984-1985

	No. Patients	No. Admits	Mean Admits/Case	Mean Charge/Day (SD) [†]	Mean Total Charge (SD)	Mean Total Length of Stay (Days) (SD)
Jan-Jun 1984						
Total	977					
No. with full bills and non-flat pricing	414	699	1.6	\$742 (\$507)	\$21,514 (\$16,910)	40 (39)
Jul-Dec 1984						
Total	1,342					
No. with full bills and non-flat pricing	629	1,070	1.7	\$639 (\$474)	\$19,516 (\$16,614)	38 (38)
Jan-Jun 1985						
Total	1,791					
No. with full bills and non-flat pricing	790	1,345	1.7	\$756 (\$538)	\$20,746 (\$17,559)	37 (37)
Jul-Dec 1985						
Total	2,349					
No. with full bills and non-flat pricing	1,097	1,922	1.8	\$734 (\$477)	\$19,249 (\$15,943)	34 (32)
Total no. with full bills and non-flat pricing	2,930	5,036	1.7	\$721 (\$498)	\$20,030 (\$16,672)	37 (36)
Total	6,459					

*Excludes flat-rate hospitals, see text for explanation.

[†]SD = standard deviation.

45% of the entire patient group for analysis. Over the four cohorts, the mean number of admissions within one year increased from 1.6 to 1.8. The mean charge per day shows some limited variation but was essentially the same for the first and last cohorts. The mean total length of stay declined over time. The total charge had a slight downward trend, which represents the composite effect of an increase in the number of admissions, a decrease in length of stay, and relatively stable charges per diem.

Table VI contrasts charge and length of stay data for the January-June 1984 and July-December 1985 cohorts for the 12-month period after the first HIV admission. These data have some extreme high values that distort the mean; as a result, the median appears to be a better indicator of central tendency than the mean. Charges per diem in New York City exceed those in the rest of the state; however, the total length of stay is nearly identical. The total charge difference therefore is primarily a function of higher charges in New York City. Statewide, the median total charge for all inpatient care within one year of the first HIV admission increased only slightly in terms of absolute dollars (\$14,600 to \$14,763), which represents a decline in terms of 1984 dollars.

DISCUSSION

When interpreting the data presented here or when making comparisons with other studies, it is important to remember that this presentation includes both AIDS- and HIV-infected patients. On the basis of the retrospective coding of 1984 and 1985 admissions (in accordance with the 1986 revision of the ICD-9-CM code), we estimate that, at first admission, approximately 13% of the cases may best be characterized as HIV infected, in that they did not meet the CDC AIDS definition. (In subsequent admissions, many of these cases met the CDC AIDS criteria). The presence of these non-AIDS admissions may cause the demographics, utilization, and costs data for patients in this study to be different from surveillance data and investigations of only AIDS cases. In addition, to obtain representative billing and utilization data, a large proportion of the cases had to be eliminated.

The results of this study were compared to the survey work done by Andrulis et al in the two national samples gathered for 1985³ and 1987.⁴ The variables analyzed in this investigation and in that of Andrulis et al were not

identical; however, for instances in which comparability appears to exist, contrasts will be made. All comparisons with 1987 data will be limited to the Northeast total values reported by Andrulis et al to minimize the impact of regional variations. The patient groups were very similar, with approximately 84% males in this study population compared with 81% in 1987 for Andrulis et al. Comparisons between the percent distributions by age for age groupings of 20-29, 30-39, and 40-49 years were within three percentage points for each group.

For the last cohort of 1985, we found a mean charge per diem of \$670 (all facilities); this compares with the 1987 figure reported by Andrulis et al of \$789 (charge data were not reported for 1985 by Andrulis et al). In this study, the mean total charge per year for the last cohort of 1985 was \$19,130, compared with \$24,775 found by Andrulis et al in 1987. Adjusting 1985 dollars to 1987 dollars brings the two studies' figures into closer agreement.

This investigation also identified regional differences in charges, with facilities in New York City charging

TABLE VI. Charge and Length of Stay for Two Cohorts One Year From First Admission

		Charge/Day	Total Charge	Total Length of Stay (Days)
Jan-Jun 1984				
Total	Mean	\$660	\$19,722	40
	Median	\$579	\$14,600	27
New York City	Mean	\$668	\$20,581	39
	Median	\$581	\$15,486	28
Rest of state	Mean	\$593	\$16,346	44
	Median	\$534	\$12,184	27
Jul-Dec 1985				
Total	Mean	\$670	\$19,130	36
	Median	\$627	\$14,763	25
New York City	Mean	\$673	\$19,617	37
	Median	\$632	\$15,388	25
Rest of state	Mean	\$635	\$16,435	35
	Median	\$572	\$12,106	24

more than those in the rest of the state. It is important to note that the analysis of median and mean indicates that the mean is biased toward the high side, and perhaps is not the best estimator of central tendency for the population. The total mean length of stay for one year for this study group was 36 days with a median value at 25 days. Andrulis (1985) found the average to be 32 days with a range of 2–200 days. The data set presented here reveals a mean number of admissions per year of 1.8 for the last cohort of 1985; Andrulis (1985) reported 1.6 admissions per patient per year. Due to fundamental linkage problems discussed above, the HIVLF is acknowledged to be imperfect; however, the values obtained appear to be consistent with those obtained by carefully designed and executed sample surveys.

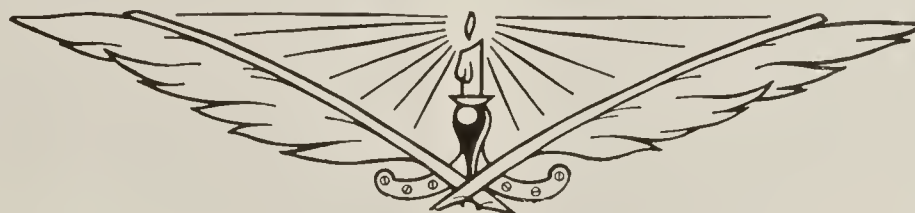
HIV/AIDS has gone from an unidentified condition to one of the major public health problems of recent history in only a decade. Health policymakers not only need to be sensitive to the historical and changing pattern of affected population groups, but also must keep pace with the continuing improvements in therapy and the impact of prevention efforts. Improved diagnostic and treatment procedures and the introduction of new chemotherapeutic agents will continue to influence resource requirements and patterns of care. The availability of both inpatient and outpatient resources must be adjusted to reflect changes in clinical management and service utilization. The results of this investigation

will form a foundation for comparison with future acute care resource consumption in New York State.

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Right-lower-quadrant mass and elevated serum carcinoembryonic antigen level

CASE PRESENTATION

Harlan D. Alpern, MD (Pathologist-in-Chief): It is a pleasure today to present a special surgical CPC with the principal discussant, Dr William Stahl, visiting Professor of Surgery from New York Medical College.

John E. Olson, MD (Attending Surgeon): A 66-year-old woman was admitted to Mary Imogene Bassett Hospital to undergo surgical abdominal exploration for an enlarging right pelvic mass associated with occult blood in the stools, a rising serum carcinoembryonic antigen (CEA) titer, and an elevated serum alkaline phosphatase level.

Twenty-one months prior to this admission (PTA), the patient had undergone a superficial parotidectomy at this hospital, for a benign lymphoepithelial lesion of the left parotid gland. At that time, an 18-mm mass was identified in the right breast, with overlying molded skin retraction; on needle biopsy, the lesion proved to be an adenocarcinoma. In addition, mammography identified a 13-mm seemingly benign mass in the left breast. There were no clinically involved axillary lymph nodes, and no clinical, chemical, or radiographic evidence of metastatic disease. The patient's serum level of CEA at that time was 4.8 ng/mL (normal range, 0–3 ng/mL).

The 18-mm right breast carcinoma was locally excised, together with axillary dissection, followed by primary radiation therapy to the breast. Twenty-six lymph nodes were examined and were free of metastases. Estrogen and progesterone receptors were strongly positive in the tumor, 672 and 552 fm/mg of cytosol protein, respectively. The patient received no adjuvant hormonal therapy or chemotherapy.

Six months after completion of radiation therapy, (12 months PTA), the patient remained clinically free of disease. Post-treatment mammograms revealed no abnormality of the treated breast and no change in the 13-mm density in the left breast. The chest film, complete blood cell count, and blood chemistries were all normal, except for the serum CEA, which had risen from 4.8 ng/mL to 7.7 ng/mL; the serum alkaline phosphatase level was slightly elevated at 154 U/L, above the pretreatment level of 105 U/L (normal range, 50–136 U/L).

Nine months PTA, the patient was clinically well, with no apparent recurrence of her breast cancer; but her serum CEA had further increased to 9.0 ng/mL, and the

serum alkaline phosphatase was now 195 U/L. There were no other significantly abnormal serum chemical determinations. Her hematocrit was 37%. Two of two stools were positive for occult blood. Colonoscopy to the midtransverse colon revealed multiple diverticula of the sigmoid colon and a 1.5 × 1.5 cm sessile polyp of the upper rectum, 12 cm above the anal verge. An air-contrast barium enema failed to reveal additional lesions; on removal, the rectal polyp proved to be a benign villotubular adenoma. It was suspected that this benign lesion might not adequately explain the elevations of serum CEA and of serum alkaline phosphatase or the presence of occult blood in the stool. Shortly thereafter, upper gastrointestinal endoscopic evaluation was reported to be normal.

Seven months PTA, mammograms revealed no recurrence of the conservatively treated right breast cancer and no change in the benign-appearing density in the left breast. The computed tomography (CT) scan of the abdomen and pelvis indicated no evidence of metastatic disease, but did disclose a 4–5-cm cystic structure, which had the density of water, in the right adnexal region.

RADIOLOGIC PRESENTATION

Stephen Hughes, MD (Attending Radiologist): One film from the barium enema performed nine months PTA demonstrates a possible abnormality in the right lower quadrant. The spot film of the cecum and the terminal ileum shows partial but incomplete filling of the appendix, which can be found in about 20% of healthy people. Consequently, this lack of complete filling has no definite significance, in the absence of any clinical suspicion that the appendix is abnormal. The barium enema did not reveal any significant mass effect in the terminal ileum or base of the cecum.

The CT scan of the abdomen and pelvis, taken seven months PTA, shows a large, partially cystic mass in the right iliac fossa, just below the psoas muscle and medial to the cecum: It extends lower into the pelvis, to the level of the right ovary. This mass possibly represents a cystic ovarian neoplasm.

Dr Olsen: Seven months PTA, the patient's pelvic examination was reported as negative by a consulting gynecologist, who felt no masses in the adnexae, and who initially did not express concern about the observed CT abnormality. At this time, tests for occult blood in the stool, following removal of the polyp, were negative.

Five months PTA, however, the patient's serum CEA remained elevated at 9.5 ng/mL; the serum alkaline phosphatase was stable at 148 U/L, and a repeat CT scan

Based on a clinical conference held at Mary Imogene Bassett Hospital, Cooperstown, NY, on March 21, 1990.

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of the pelvis (Fig 1) revealed no change in the density in the right adnexa. It was considered at this time that this lesion was most likely an ovarian cyst. A pelvic ultrasonogram was performed.

Dr Hughes: On the CT scan taken five months PTA (Fig 1), the mass appears to be separate from the right ovary. Although the films were initially interpreted as demonstrating most probably a cystic ovarian neoplasm, in retrospect, this scan shows that the mass is not of ovarian origin.

Dr Olson: Is the density of that mass totally homogeneous? It appears to me as though the density of the mass is heterogeneous.

Dr Hughes: It is very inhomogeneous, and there are some septations in it. On the ultrasound of the right lower quadrant (Fig 2), the right ovary appears slightly enlarged, to about 3-cm in maximum diameter, but there is no cystic mass related to the right ovary. I think then that this partially cystic mass in the right-lower-quadrant is not of ovarian origin.

Dr Olson: Five months PTA, the patient's condition was reevaluated; again tests for occult blood in the stool were positive. Repeat colonoscopy, carried out by Dr Davis, with complete visualization to the cecum, revealed several areas of angiodysplasia near the ileocecal valve. A small polyp in the descending colon was completely excised, and one in the ascending colon was partially excised; both polyps were histologically benign.

Three months PTA, the patient was found to be well but continued to have occult blood in the stools, with a stable hematocrit of 38%. Her serum CEA level was increased slightly to 9.8 ng/mL. Her serum alkaline phosphatase was still elevated at 174 U/L.

After a three-month absence from the country, she again appeared to be well, without any physical evidence of disease. Her serum CEA was now 12.4 ng/mL; the alkaline phosphatase was slightly elevated at 145 U/L; the serum CA-125 ovarian antigen, a marker for ovarian carcinoma, was within normal limits. There were no other significant abnormalities of her blood chemical determinations. The chest film, bone scan, and upper



FIGURE 1. CT scan of abdomen, five months prior to admission, showing cystic mass in right iliac fossa (arrow).



FIGURE 2. Ultrasonogram of pelvis, five months prior to admission, showing right ovary (arrow) without associated cyst or mass.

gastrointestinal and small bowel barium studies were all within normal limits.

An in-depth review of the case was presented at our Tumor Conference, and questions were raised as to whether the lesion could be a mucocele or a carcinoma of the appendix, rather than an ovarian cystic lesion, as had been previously suggested. Surgical exploration was recommended. Just prior to surgery, a repeat CT scan now showed a change in the character of the mass.

Dr Hughes: In this preoperative CT scan, new free fluid is visible in the pelvis, especially in the cul-de-sac (Fig 3). This fluid might be ascites or might be due to rupture of the right-lower-quadrant mass. CT images higher in the abdomen did not disclose any free fluid in the paracolic gutter or elsewhere. The septations in the mass itself appear to have increased in size (Fig 4).

William Stahl, MD (Professor of Surgery, New York Medical College): It is interesting to speculate that if this woman had not previously had an otherwise unrelated disease, you would not have discovered this right lower quadrant mass at all, even up to the time of her last admission because she had no symptoms. The discovery of the mass was a fortuitous finding during the course of



FIGURE 3. Preoperative CT scan of abdomen, showing new fluid collection within pelvis (arrow).



FIGURE 4. Preoperative CT scan of abdomen, showing enlarging mass (arrow), with increase in septations, in right iliac fossa.

other investigations, which uncovered the elevations of her CEA and the serum alkaline phosphatase.

The aspect of the case that distresses me is the presence, in a 66-year-old lady, of a right-lower-quadrant cystic mass, initially reported to be in the ovary. As a general surgeon, I would have been worried about this lesion because of the high incidence of malignancy arising in the ovary. When the CT scan eventually showed clearly that the mass was not in the ovary, but rather represented some other intra-abdominal condition, that finding would have concerned me even more.

What could this lesion have been? A mucosal lesion in the bowel was not seen during an adequate colonoscopy, in spite of the intermittently guaiac-positive stools, which could have been caused, of course, by the colonic polyps. However, there were chemical abnormalities and an abnormal radiologic finding that could have been associated with a lesion of the cecum or of the appendix.

Having previously seen only one film of the barium enema, I was nevertheless concerned about the condition of the cecum. When the cecum is radiologically studied, it is important to know whether it has or has not been filled and has it been completely or only partially filled. With only one radiographic view of the cecum, you cannot be certain as to the presence of a lesion or lesions in that region.

In this circumstance, I would have expressed my concern that the cecum did not expand and fill completely to my satisfaction during the barium enema procedure. This would raise the possibility of a lesion extrinsic to the cecum. Unless other films clearly show adequate filling of the cecum, the appearance of this one film, together with the presence of a cystic mass and only partial filling of the appendix with barium, would have suggested that the lesion might be related to the appendix, rather than to the ovary.

Lesions of the appendix include adenocarcinoma, various mucus-producing tumors, and mesenteric-type lesions, all of which can be treated surgically. I believe that I would have been tempted to operate on this

patient six or eight months earlier than was done, when the first scan showed an unexplained cystic mass. However, that would have been the only difference between your and my approach to this problem. I would not have been able to pinpoint a definite preoperative diagnosis any better than you were.

CLINICAL DIAGNOSIS

Right pelvic cystic mass. Dr Olson: Surgical exploration was performed on February 22, 1989. We did not find a primary ovarian neoplasm but rather a mass in the right side of the pelvis, which was a confluence of the appendix, the right fallopian tube, and the right ovary. The appendix itself was enlarged, dilated, and bulbous, measuring about 7 cm long and 2 cm in diameter, with a 2-cm perforation near its tip; about 150 ccs of mucinous material was pooled in the pelvis. There were a few very tiny, 1–2 mm, translucent mucinous nodules implanted along the right side of the mesentery of the rectosigmoid colon and along the posterior pelvic peritoneum overlying the right ureter. The right tube and ovary were adherent to this mass.

The appendix and the right tube and ovary were all removed in continuity and submitted to the Department of Pathology for frozen section. There were no other abnormalities elsewhere in the abdomen and no other evident implants elsewhere.

PATHOLOGY PRESENTATION.

Harlan D. Alpern, MD (Pathologist-in-Chief): Frozen section of the dilated vermiform appendix demonstrated abundant gelatinous mucinous material in the lumen. The appendiceal mucosa was lined by a benign, mucin-producing neoplastic epithelium.

Dr Olsen: At surgery, it was apparent that this was not a simple mucocele of the appendix that had ruptured to cause pseudomyxoma peritonei but was a neoplasm of the appendix with extension to the level of transection of the appendix. In addition, because she had angiodysplasia of the right colon and an incompletely resected polyp in the right colon, we elected to perform a right hemicolectomy, followed by an omentectomy, removal of the opposite ovary, and excision of the peritoneal implants in the pelvis. When this was completed, there was no residual gross disease; throughout the operation, the peritoneal cavity was irrigated.

We had discussed the treatment of pseudomyxoma peritonei recently at the Eastern Cooperative Oncology Group Surgical Committee meeting, including the suggested use of intraperitoneal chemotherapy. During the course of the surgery and at the end, I called our consultant in colorectal surgery at Roswell Park, to ask his advice concerning intraperitoneal chemotherapy. He advised against it, since there was no gross residual disease. Therefore, we did not insert a catheter for subsequent chemotherapy.

Dr Alpern: The appendix was dilated, measuring 5 cm in diameter and 5 cm long due to the presence of cysts (Fig 5). The lumen was filled with gelatinous mucinous material. Adherent to the appendix was the right fallopian tube and ovary. Multiple sections of the dilated appendix demonstrated a mucinous cystadenoma, which

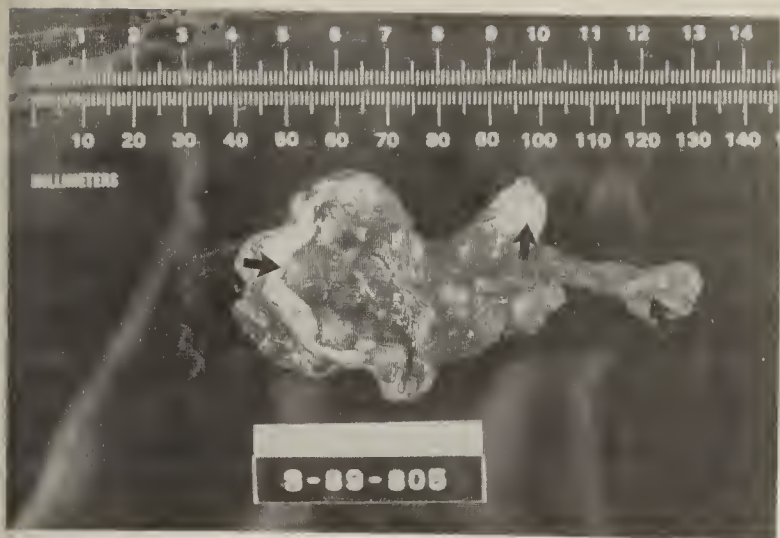


FIGURE 5. Operative specimen, including cystically dilated appendiceal mass (left arrow), adherent right ovary (middle arrow), and right oviduct (right arrow).

is a benign neoplasm, composed of a tall columnar benign neoplastic epithelium (Fig 6). The nuclei were slightly enlarged and hyperchromatic, with some pseudostratification and occasional mitotic figures. There was no cytologic evidence of malignancy and no invasion into the appendiceal wall. In some areas of the cystic mass there was no epithelial lining, only a foreign-body type giant-cell reaction to the mucin, with associated slight chronic inflammation. In sections stained for neutral mucin by periodic acid-Schiff (PAS) with diastase and for acid mucin by mucicarmine, mucin was identified in the neoplastic epithelium and in the appendiceal lumen.

Cytologic examination of the fluid within the mass demonstrated acellular gelatinous material containing tiny calcifications. The peritoneal implants demonstrated mucinous material and a mesenchymal reaction to the mucin, but no evidence of neoplastic epithelial elements. These peritoneal implants represent pseudomyxoma peritonei.

The ileal segment was 14 cm in length, and the segment of cecum and large bowel was 20 cm in length. Two tubular adenomas were found in the right colon. The multiple lymph nodes in the small and large intestine were without evidence of metastases. The

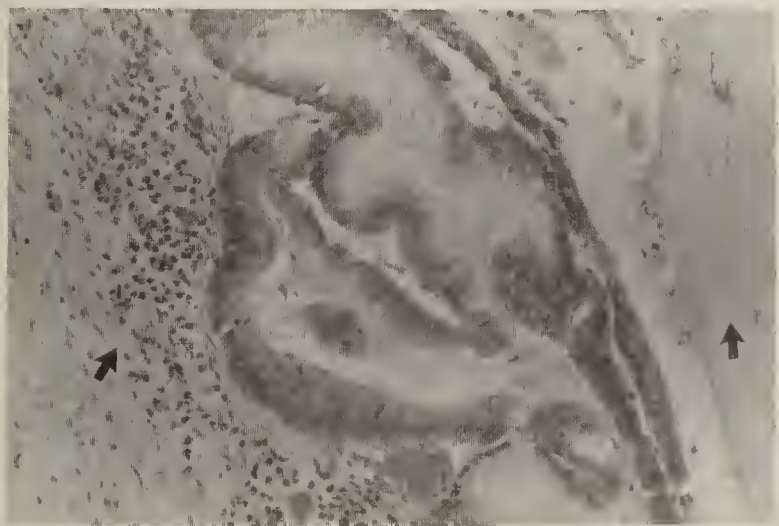


FIGURE 6. Section of dilated appendix, showing benign neoplastic columnar epithelium, appendiceal muscularis propria with inflammatory cells (left arrow), and mucus collection in appendiceal lumen (right arrow) periodic acid-Schiff stain; (original magnification $\times 200$)

ovaries were atrophic with corpora albicantia present and demonstrated no metastases.

The vermiform appendix is susceptible to the same neoplasms that occur in the colorectum. However, being a small organ, appendiceal neoplasms are rare. Mucin production by benign and malignant epithelial neoplasms within the confined space of the vermiform appendix frequently produces cystic dilation and formation of the so-called mucocele of the appendix.¹ Mucocele is a nonspecific term that refers to the distention of part or all of the vermiform appendix by accumulations of mucus in the lumen. It may occur as a result of a simple non-neoplastic luminal obstruction, or as a result of a benign or malignant neoplasm. The simple non-neoplastic obstructive mucocele is generally less than 1 cm in diameter. The common benign glandular neoplasm of the appendix is referred to as a mucinous cystadenoma.¹ It is grossly characterized by a cystically dilated spherical or sausage-shaped appendiceal mass filled with viscous mucus. Calcifications may occur in the mucus, which in some cases may be large enough to form a calculus; this can be demonstrated radiologically.

The mucinous cystadenoma occurs with approximately equal frequency in men and women, and over a wide age spectrum. These tumors may be symptomatic or may be discovered incidentally at laparotomy for another condition.

As with colorectal tumors, adenomas of the appendix may have tubular, villotubular, or villous architecture. In some instances, the pressure of the intraluminal mucin may produce flattening of the epithelium. Epithelial dysplasia may also be present. These adenomas are preinvasive neoplasms that may progress to adenocarcinoma or cystadenocarcinoma. They are associated with synchronous or metachronous adenomas and carcinomas elsewhere in the colorectum. This patient did have two synchronous tubular adenomas in the right colon.

In one series, about 20% of patients with mucinous cystadenomas of the appendix were found to have an associated separate primary adenocarcinoma of the colorectum.² Thus, the finding of an adenoma of the appendix should prompt screening of the entire colorectum for malignancy.

Tumors of the appendix, both benign and malignant, may be associated with the escape of mucus through an attenuated or ruptured appendiceal wall into the peritoneal cavity. This condition is referred to as pseudomyxoma peritonei.¹ This process may be localized to the right iliac fossa or be generalized in the peritoneum. When the underlying lesion is a benign mucinous cystadenoma, as in this patient, generally the condition is localized and regresses following resection of the primary tumor. If the underlying lesion is a mucinous cystadenocarcinoma, the peritoneal involvement is generally diffuse and often progressive, and ultimately fatal in most cases, with fibrous adhesions of the peritoneal cavity leading to intestinal obstruction.

Dr Stahl: From the surgical point of view, this is an interesting lesion of the appendix. It can be either obstructive with a mucus collection or a cyst, or it can be neoplastic and either benign or malignant. There are numerous individual case reports of this type of lesion,

but there are not many large series in the medical literature; in fact, it is a rare lesion.

Of the few series that include significant numbers of such lesions, that is, as many as 50 or 60, the incidence of mucin-producing adenocarcinoma is quite low, representing only approximately 5%–10% of the total.³⁻⁵ Most of the reported lesions are histologically benign. Clinically, the obstructive lesions are most often found incidentally, consisting of a small nodule, 1–2 cm in size, and unaccompanied by symptoms. About 60% of benign cystadenomas and malignant cystadenocarcinomas present with abdominal pain or a mass.

In this patient, the lesion appears to be of the benign neoplastic type that did not yet present symptoms, but perhaps would have progressed to the formation of a clinically evident mass or would have caused pain at some point. In 1980, the M.D. Anderson Center reported 30 cases (1954–1978) of pseudomyxoma peritonei, which represents the ultimate spread of this lesion within the peritoneal cavity.⁵ In the malignant cases, the five-year survival was 54%, and the ten-year survival was 18%; when the malignant tumors rupture, the prognosis is unfavorable. This report indicated that postoperative radiation therapy improved the five-year survival in a small number of cases, whereas the addition of chemotherapy did not.

When this series was initially presented, Dr Brad Aust reported his experience with Dr Owen Wangenstein in the performance of second-look operations, which consisted of initial resections (primarily for colon cancer), reexploration after six months, no matter what the clinical condition of the patient. This second-look operation preceded the availability of CT scans, which can now so readily identify enlarged lymph nodes and other evidence of metastases. Such evidence of spread or recurrence were looked for grossly at the second-look operations, and if found, were resected, along with periaortic node resection. If this search identified neoplastic tissue, six months later an exploratory procedure was again performed on this patient.

In several patients on whom Dr Wangenstein operated five or six times in this way, eventually no tumor was found. It was of course a small decreasing number of such patients, but Dr Wangenstein felt that he could rid some of these patients of their tumor.⁵ This second-look procedure was not taken up as a serious project by other surgeons.

In 14 patients that Dr Wangenstein treated for pseudomyxoma peritonei, he performed 37 second-look procedures. During the second-look on patients with mucinous adenocarcinomas and pseudomyxoma peritonei, three of the patients were free of tumor at six months and thereafter stayed well. For the remaining 11 patients, he was able to rid four of gross tumor by repeated second-look procedures.⁵

We should not forget that in the case of malignant pseudomyxomas, although they may be debulked with omentectomy and at least with appendectomy or right colectomy, as well as with bilateral oophorectomy in the female, subsequent radiation therapy may be indicated. In addition, we might even consider a second-look procedure in such patients.

Dr Olson: On clinical follow-up, this patient had negative CT scans of the abdomen and pelvis at two months and at eight months after the surgery. About one year later, she remains free of disease with normal serum CEA and serum alkaline phosphatase levels and with negative tests for blood in the stool. She is clinically evaluated here when she is in this country, although she has been in Spain most of the time.

James Bordley III, MD (Attending Surgeon): If the CT scan again became positive, what would you do?

Dr Olson: I'd operate on her.

Dr Bordley: And this time would you insert a catheter for possible chemotherapy?

Dr Olson: Possibly I would, but I am not sure. There are experienced surgeons who will spend 12–14 hours resecting every last little implant in such cases. Most of the lesions that were discussed in the Surgical Committee were malignant, with grossly evident disease. I was very surprised to find that we were able to clean out all the visible mucinous lesions in this patient. There were only a very few of the small 1–2-mm implants, which on excision were not neoplasms.

Dr Alpern: Those implants were only mucus on histological analysis. There were no glandular cells within them.

Dr Olson: Therefore, I think that that finding decreases even more the chances that this type of lesion may recur in this patient.

Dr Bordley: What would you do if there was evidence of recurrence?

Dr Olson: I would resect the tumor again.

FINAL ANATOMIC DIAGNOSES:

Mucinous cystadenoma, vermiform appendix, ruptured, with pseudomyxoma peritonei.

Abdominal lymph nodes, negative for malignancy.

Atrophy and adhesions, right ovary and oviduct.

Tubular adenomas, two, right colon.

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How we tell our doctor about pain

JACQUELINE GALLOWAY

Although some patients are comfortable describing pain to their doctor, I noted that on my first visit to a doctor, particularly if my pain seemed chronic or predictably progressive, I shifted to an attitude of stoicism and minimized my pain.

It is not unusual for many of us to have a deep need for our doctor to like us. If we follow through with that view and have hesitation in revealing details of our pain, we not only defeat our needs by downplaying our description of pain, but also limit our physician's ability to diagnose and treat us accurately. When chronic illness manifests in adulthood, our perception of pain is usually genuine and exact. However, since we also have a deep need for approval from our doctor, we as patients often express embarrassment or feel a sense of failure with pain that persists beyond the treatments prescribed.

At home or in social and business settings, whether we experience pain or not, we often respond to those who know we have an illness and politely ask how we are, with the perfunctory "fine, thank you." Many of us learned to avoid discussing pain when growing up. By the time we were teenagers, we shunned or placated those who dwelt on their broken arm or a short-lived illness. It was plainly uncomfortable after we responded to that first sentence "I have so much pain."

As a professional figure skater in the mid-1950s, I sustained a dislocated patella and a fractured femur. Once my cast was removed and I began physical therapy with ongoing improvement and ultimate success, both my doctor and I developed a different bonding, as if my cure were the impetus to a better relationship. I base this observation on the fact that when I subsequently reinjured my knee, my recovery was complex, and the prognosis included the tragic termination of my skating career. I began to sense that my doctor's attitude (the same physician I had previously) at each office visit was not as enthusiastic, and I felt as if I had somehow failed him.

Human nature being what it is, we tend to retain certain experiences. Several decades later, when I was diagnosed with fibromyalgia and degenerative spinal disease, I was reluctant to disclose every detail of my pain and decided to underrate it, especially during the first visit to the doctor. What I encountered, however, was a well-developed, systematic inquiry that relieved me of the burden I had feared. As the doctor probed

both verbally and later during the physical examination, I sensed that I was not entirely responsible for detailing my pain. There was a considerable difference in my new doctor's evaluation of my pain from what I remembered from previous years.

Instead, I had in my new physician, an expert in pain management, and it was the questions put directly before me that seemingly made the examination and evaluation the doctor's inquiry and not solely my long list of complaints. Questions were specifically directed at what increased my pain and its severity. My physician was precise and thorough, and I began to relax with the burden of talking about pain redirected by way of questions and answers. I no longer feared how I would be perceived by the doctor. I was not only asked when the pain started, but also if it had gotten worse in time, if it were intermittent or constant, and if it came in waves and then subsided. We talked about how my sleep and other activities were affected, whether I had ever experienced this "kind" of pain previously, and what increased the pain (ie, sitting, lying down, walking?) Did the pain distract me or could I distract myself from the pain? Or, was the pain so intense that distraction was impossible? Did the pain cause me to be irritable, angry, or depressed? He elicited details about what accompanied the pain, such as nausea, inability to breathe, or perspiring. We discussed the medication I had taken and then details concerning pain intensity and characteristics, such as pulsating, throbbing, shooting, sharp, hot, dull, aching, radiating, and so on.

During the examination, I tried to sort out my thoughts about pain and instead of being concerned about how the doctor viewed me, I felt secure and had a sense that trust was gradually being established. I no longer had difficulty spontaneously answering every question about pain. I also began to realize that the tools of an accurate diagnosis must by necessity include the language of the patient's characterization of symptoms. To my amazement, I was eagerly cooperative during that first visit, while the questions continued.

What was it that once made me act obscure, nonchalant, or stoic when discussing pain? Was it something about losing control? Was I concerned about being a "good patient?" In retrospect, I conclude that my perception was an acquired obstacle from either one doctor's way of dealing with my injury years ago or simply an outdated general attitude that has been partially eliminated by sensitive current medical school teaching methods. I have taken time to search within for

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what motivated me to once feel so uncomfortable about discussing pain. Some thoughts of anxiety about pain were present, a certain amount of denial existed, and I was concerned about being considered a "troublesome complainer." However, at the core, I maintain that a doctor's attitude when asking about pain directly influences the patient's response.

A somewhat curious dichotomy is that medical insurance "rewards" illness. I surely did not receive any "benefits" for all the years I was well and not in need of regular medical care, physical therapy, sophisticated tests, and costly medications. Now that I have a serious, chronic illness, my insurance company pays close attention to me with not only a readiness to pay for my expensive treatments, but also with disability payments.

Illness has not only changed my life, but has also sharpened my discernment and responses, particularly with my doctors. I read enough psychology books claiming that stress, crisis, grief, and shock are the cause of everything from back pain to cancer. There might be some validity to those theories, but I began to consider that the reality of our humanness included obstacles such as illness, and I came to regard my sickness as being either a struggle or a challenge. It was simply a choice I had to make. I also searched to capture in a word or two the key to dealing with daily pain. It was not merely tolerance, although I tested that. When I found it, it unlocked the mystery of pain for me. That key in seeking relief had to include being truthful to myself and my doctor and risking my imagined idea that I would be considered a whiner or worse. My doctor was not astounded by my list of agonies during subsequent visits. In fact, with my honesty and openness, a special trust unfolded in which I was the key holder.

There was a time when I accepted pain as inevitable and inescapable. The problem with that premise is that no magic could change the pain. As the trust between my doctor and me deepened and pain relief modalities were tried, not all were successful, but at the core of pain remained something almost mystical. In my search, I found that in the virtues of trust and faith there was a reward of patience and peace.

Dealing with pain involves trust. We cannot use rules by which ordinary measures are taken. We evaluate this trust with our endurance, tolerance, and obedience. The trust about which I speak involves a faithfulness to our state in life, being true to ourselves.

When we are ill, if we are in pain, or if we are dying, our faithfulness should be our primary focus. We should not focus on mystical cures, but rather deal with the reality that pain is part of the human condition of life.

As I established that distinctive faith in my doctor, I discovered within more tolerance to pain, and it was no longer my primary focus. Pain need not be unmanageable; pain relief can be as essential as maintaining electrolyte balance and emotional stability. Extending trust then to our medication and our physician's expertise and trusting in our ability to cooperate and endure should be exemplary goals.

When I exhausted the search to discover possible reasons for my disease, which are unascertainable, I was ready to discover and develop insight into being faithful and having trust. Being faithful involves compliance in following prescribed medical treatments and protocols, a regime of a sound diet, sensible and appropriate exercise, and trusting the person guiding our health—our doctor. Our doctor's responsibility ideally will lead us to our responsibility. Our faith in our physician is directly related to the faith our physician has in us.

Acute appendicitis secondary to Kaposi's sarcoma in the acquired immunodeficiency syndrome

STEFANO RAVALLI, MD; RAF A. VINCENT, MD; HOWARD L. BEATON, MD

Kaposi's sarcoma (KS) is the most common neoplasm associated with the acquired immunodeficiency syndrome (AIDS), although its incidence appears to be declining for unclear reasons. In association with AIDS, KS occurs predominantly in homosexual males and pursues an aggressive course with extensive cutaneous disease and frequent extracutaneous involvement. The gastrointestinal tract is frequently affected, but involvement is almost always asymptomatic. Primary visceral KS, in the absence of skin lesions, has only rarely been described in the literature. We describe two cases of acute appendicitis secondary to appendiceal localization of KS. In one of the patients, no cutaneous lesions were found at the time of presentation.

CASE REPORTS

Case 1. A 23-year-old homosexual man presented to Beth Israel Medical Center with complaints of abdominal pain, fever, and chills for three days. The patient was known to be HIV-positive since February 1986 and was asymptomatic until January 1987 when he developed oral candidiasis. In March 1988, he was noted to have a nontender cervical adenopathy and was started on zidovudine (AZT), 200 mg every four hours, as well as aerosolized pentamidine for *Pneumocystis carinii* pneumonia prophylaxis. There were never any diagnoses of other opportunistic infections, and there had been no evidence of cutaneous or mucosal lesions of KS. During the 3-4 months prior to this admission, he experienced occasional diffuse abdominal pain, with no other associated symptoms.

On admission, his blood pressure was 130/80 mm Hg; pulse, 120/min; and temperature, 40.0°C rectally. On physical examination, the abdomen was diffusely tender, more markedly in the right lower quadrant, with guarding and rebound tenderness. No bowel sounds could be heard. The rectal examination revealed a tender, large anterior mass bulging into the rectal vault. The guaiac test was negative.

An abdominal radiograph showed scattered, dilated small bowel loops with no definite evidence of obstruction; no free air in the peritoneal cavity was noted. Chest films and flexible sigmoidoscopy were within normal limits. A computed tomography (CT) scan revealed a large pelvic mass consistent with an abscess. Pertinent laboratory data included a white blood cell count of 4,300/mm³ with 37% polymorphonuclear leukocytes, 32% band forms, and 28% lymphocytes; hemoglobin, 11.5 g/dL; hematocrit, 34.8%; and amylase, 37 IU/L (normal range, 25-115 IU/L).

The patient underwent an exploratory laparotomy. At surgery, the appendix was found to be perforated with the formation of a pelvic abscess containing approximately 300 cc of pus. An appendectomy with abscess drainage was carried out without complications. The microscopic examination of the resected appendix revealed the classical features of KS (Figs 1, 2), consisting of numerous slit-like vascular spaces and proliferation of atypical spindle cells.

The postoperative course was complicated by fever up to 40.0°C for about one week, which gradually subsided with intravenous antibiotics. Blood cultures were repeatedly negative. The patient was discharged in good condition on the 15th postoperative day. At a follow-up office visit approximately one month after discharge, cutaneous KS lesions were noted for the first time.

Case 2. A 30-year-old homosexual man was admitted to Beth Israel Medical Center because of fever, crampy abdominal pain, and constipation. The patient had been diagnosed with AIDS in 1985, when he presented with oral thrush. His medical history was also significant for oral hairy leukoplakia and anal warts. Six months

prior to admission, he was noted to have cutaneous KS that, in spite of chemotherapy and radiation treatment, rapidly spread over his body with simultaneous involvement of the oral cavity. He did well until one week prior to this admission, when abdominal pain, mainly localized to the lower quadrants developed, accompanied by vomiting and diarrhea. On admission, he had a blood pressure of 110/70 mm Hg; pulse, 100/min; and temperature, 39.8°C rectally. The abdomen was slightly distended and diffusely tender, with guarding and rebound tenderness; bowel sounds were absent. Abdominal films showed considerable dilation of the small bowel with air-fluid levels but no free air. The chest film was normal. Significant laboratory data included a white blood cell count of 14,300/mm³, with 92% polymorphonuclear leukocytes; hemoglobin, 12.8 g/dL; hematocrit, 37.1%; blood urea nitrogen, 42 mg/dL; creatinine, 2.4 mg/dL; amylase, 59 IU/L (normal range, 25-115 IU/L). He underwent an exploratory laparotomy. At surgery, a perforated appendix was found along with diffuse suppurative peritonitis.

Microscopic examination of the resected appendix revealed appendiceal involvement by KS. The postoperative course was complicated by an intraabdominal abscess (Fig 3), which was percutaneously drained under CT scan guidance. Cultures of peritoneal fluid and abscess contents grew *Escherichia coli*. A large, right-sided pleural effusion also developed, necessitating a therapeutic thoracentesis. The patient was discharged in stable condition on the 42nd postoperative day.

DISCUSSION

KS, a multicentric neoplasm of uncertain histogenesis, has been observed in four different epidemiologic settings.¹ The classical form of the disease occurs mainly in elderly white males of eastern European and Mediterranean origins; it presents as an indolent dermal growth. The African variant has a similar course in adults, whereas in children it behaves as an aggressive tumor, commonly involving

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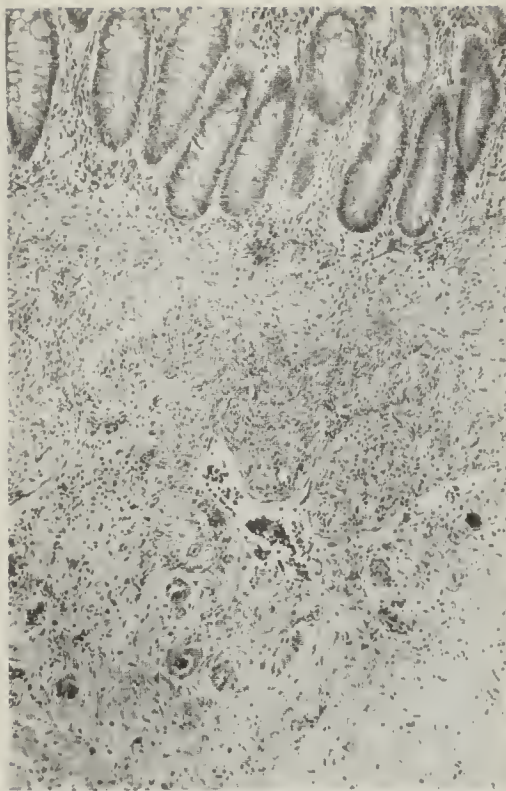


FIGURE 1. Colonic mucosa and submucosa showing spindle cell and vascular proliferation (hematoxylin and eosin stain; original magnification $\times 80$).

lymph nodes and the viscera. Extracutaneous involvement is also frequent in a third variant, which occurs primarily among organ transplant recipients receiving immunosuppressive treatment. Finally, KS is the most common neoplasm associated with AIDS, occurring mainly in homosexual males. Its incidence in all risk groups appears to

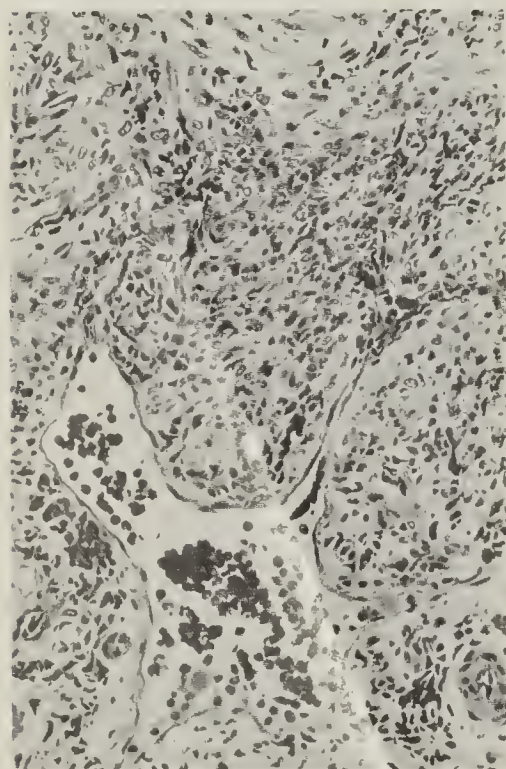


FIGURE 2. Appendix. Proliferation of slit-like vascular spaces, lined by plump endothelial cells and often containing a single erythrocyte (hematoxylin and eosin stain; original magnification $\times 200$).

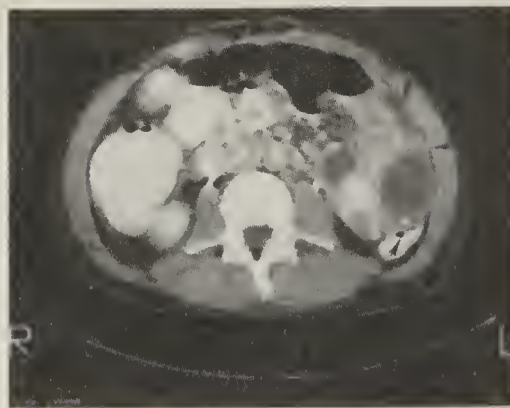


FIGURE 3. CT scan, obtained after administration of oral and intravenous contrast, revealed a large loculated fluid collection in the left lateral abdomen (arrows).

be declining for unclear reasons.² Involvement of several extracutaneous sites, most frequently the lungs, lymph nodes, and gastrointestinal tract, is quite common in patients with AIDS, and the disease usually takes a rapid and aggressive course.

Primary visceral KS (ie, in the absence of cutaneous disease) is rare, although its incidence varies remarkably among different studies. Rates have ranged from 5%⁴ to as high as 29%.⁵ The clinical manifestations of primary visceral KS have not been extensively described in the literature.⁶⁻⁹ The first patient we report here, in whom acute appendicitis occurred as a consequence of appendiceal localization of KS in the absence of cutaneous involvement, provides another example of this unusual manifestation of the disease.

In general, the gastrointestinal (GI) tract is the most common extracutaneous localization of KS. The actual incidence depends on the methods used for establishing the diagnosis. Rose et al¹⁰ reported an incidence of 48% in patients examined using radiography and endoscopy. Friedman and et al,¹¹ using endoscopy alone, found

lesions "morphologically typical" of KS in 40% of their patients. The same authors reported a postmortem incidence of intraabdominal visceral KS in 77% of patients with cutaneous manifestations of the disease. In spite of such a high incidence of GI involvement by KS, symptoms and complications are considered rare. In neither of the above-mentioned studies were clinical findings attributable to KS. Several more recent reports concerning the surgical management of abdominal diseases in patients with AIDS point toward different conclusions,¹²⁻²⁰ indicating a cumulative 10% incidence of KS at abdominal surgery, excluding diagnostic procedures (Table I).

Abdominal pain, diarrhea, and GI bleeding were the most common symptoms described by these investigators. In particular, GI bleeding seems to be a frequent clinical presentation, as was noted by Cello et al.²¹ They evaluated 37 patients with AIDS who presented with GI bleeding, and found KS to be the etiologic agent in six of 37 (16%). Considering only the upper GI tract, KS was the most common cause of bleeding, occurring in 4/13 patients (31%). Other clinical presentations of KS in the GI tract, which are more rare, although sporadically reported in the literature, include bowel obstruction,¹³ postprandial epigastric pain and dysphagia,⁶ jaundice,²² and sepsis.²³ We have previously reported a case of rectal KS presenting as a bleeding, painful polypoid mass simulating hemorrhoids, in a patient without cutaneous manifestations of the disease.⁷

Appendiceal localization of KS, manifesting as acute appendicitis, was unknown before the AIDS epidemic.²⁴ In the setting of AIDS, one case was described by Baker et al,²⁵ occurring in a patient with cutaneous and oral KS.

TABLE I. Cases of Kaposi's Sarcoma at Abdominal Surgery in Patients with the Acquired Immunodeficiency Syndrome

Author	Cases of Kaposi's Sarcoma	Total Cases	Percentage of Cases with Kaposi's Sarcoma
Barone ¹²	1	5	20
Wilson ¹³	4	35	11
LaRaja ¹⁴	2	36	5.5
Burack ¹⁵	0	10	0
Nugent ¹⁶	0	5	0
Olivier ¹⁷	1	4	25
Potter ¹⁸	1	5	20
Ferguson ¹⁹	0	4	0
Robinson ²⁰	2	6	33.3
Total	11	110	10

We have described here two additional cases, in one of which no dermatologic manifestations of the disease were present at the time of presentation. In all three patients, the clinical and pathologic features were quite typical of acute appendicitis, with the notable, although not unexpected, exception of a normal white blood cell count in two of the three patients. A perforated appendix was the rule at surgery. Finally, the postoperative course was complicated in the two patients described here by fever and intra-abdominal abscess formation, requiring a long hospital course. This is in agreement with the high operative morbidity reported by other authors¹⁹ in patients with AIDS.

Acute appendicitis is a fairly common surgical problem in patients with AIDS. In the previously quoted studies on the surgical management of patients with AIDS,¹²⁻²⁰ acute appendicitis was found in ten of 110 patients requiring abdominal surgery; KS did not play a pathogenetic role in any of these cases. Nevertheless, we are convinced that with the ever-increasing number of AIDS cases, KS appendicitis will be seen more frequently, and we suggest that it should always be considered in the differential diagnosis of an acute abdomen, even in patients without dermatologic manifestations of the disease.

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Subacute pulmonary toxicity from amiodarone

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Amiodarone is a highly effective drug for the treatment of lethal ventricular arrhythmias. Complications include skin discoloration, photodermatitis, thyroid dysfunction, corneal microdeposits, peripheral neuropathy, hepatic dysfunction, and pulmonary toxicity. Pulmonary toxicity necessitating discontinuation of the drug is a major problem, occurring in 5% to 17% of

patients and depending mainly on dosage and length of follow-up.¹ Most reported cases of pulmonary toxicity occur in the chronic phase of drug administration and present with slowly progressive cough, dyspnea, and pulmonary infiltrates on chest radiographs. Acute irreversible respiratory failure has not been described. We report two cases of acute toxicity, which occurred early in therapy and resulted in acute respiratory failure and death.

CASE REPORTS

Case 1. A 73-year-old man was given amiodarone for sustained ventricular tachy-

cardia. Procainamide and quinidine had been initiated but discontinued due to side effects. He had had multiple myocardial infarctions, and cardiac catheterization showed a diffusely hypokinetic left ventricle with an ejection fraction of 0.26 and diffuse three vessel coronary artery disease. A chest radiograph prior to the administration of amiodarone showed normal vasculature and no infiltrates. Pulmonary function tests showed normal lung volumes and diffusion capacity; the Pao₂ was 84 mm Hg.

Amiodarone therapy was initiated at a dosage of 1,200 mg daily for seven days, and was then reduced to 600 mg for five

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days, at which time the patient sustained a cardiac arrest due to ventricular fibrillation. The dosage was increased to 1,200 mg daily for six days and then reduced to 600 mg daily for seven days. Electrophysiologic studies at that time showed inducible ventricular tachycardia (cycle length, 280 ms). The amiodarone was reduced to 400 mg daily.

On the 27th day of amiodarone therapy, the patient experienced dyspnea, a nonproductive cough, and a low grade fever. A chest film showed bilateral increased interstitial markings (Fig 1). Over the next 24 hours, progressive respiratory insufficiency developed, and intubation was necessary. At that time, the pulmonary capillary wedge pressure was 10–14 mm Hg, and the pulmonary artery was 40/10 mm Hg. Cefoxitin, gentamicin, erythromycin, and dexamethasone, 10 mg intravenously daily, were initiated, but respiratory failure, a low grade fever, and extensive infiltrates on chest radiograph persisted. Bronchoscopy revealed inflammation but no purulence. Sputum cultures were negative, as were cultures of blood and urine. Bronchial alveolar lavage showed increased cellularity consisting of 39% macrophages (foam laden), 10% lymphocytes, 50% neutrophils, and 1% eosinophils. At that point, (seven days into the respiratory illness,) amiodarone was discontinued. Over the next week, his condition improved, and a chest radiograph showed partial clearing of the infiltrates. After extubation, the dexamethasone was continued. However, within 24 hours he required reintubation for respiratory insufficiency (without clinical or radiographic evidence of congestive heart failure), and he died of refractory ventricular fibrillation that same day. An autopsy was not performed.

Case 2. A 63-year-old man was given amiodarone for refractory sustained ventricular tachycardia. He had sustained an

anterior wall myocardial infarction five years prior to his first episode of ventricular tachycardia. In spite of procainamide and quinidine therapy, he had frequent episodes of ventricular tachycardia and ventricular fibrillation requiring cardioversion. Cardiac catheterization showed anteroapical akinesis with an ejection fraction of .25; right heart pressures were normal. Electrophysiologic studies showed inducible ventricular tachycardia (cycle length, 310 ms).

Amiodarone was initiated in a loading dose of 1,200 mg daily for seven days, followed by 800 mg daily for seven days, and 600 mg daily for seven days. Repeat electrophysiologic studies showed inducible but slower ventricular tachycardia (cycle length, 380 ms). A chest radiograph performed just prior to discharge showed clear lung fields, and pulmonary function tests demonstrated a normal diffusion capacity. He was discharged on 400 mg of amiodarone daily.

Approximately three weeks after discharge (six weeks after initiation of amiodarone), the patient had acute dyspnea necessitating admission to his community hospital. A chest radiograph showed diffuse interstitial infiltrates, and arterial blood gas studies demonstrated profound hypoxemia (PaO_2 40–50 mm Hg). The pulmonary capillary wedge pressure was 5–10 mm Hg. Cultures of sputum, blood, and urine were negative. A myocardial infarction was excluded by serial cardiac enzyme tests and electrocardiograms. In spite of intubation, antibiotics, steroids, and dopamine infusion, he remained hypoxemic and died of ventricular fibrillation on the third hospital day. An autopsy was not performed.

DISCUSSION

Since the introduction of amiodarone in 1969, it has proven to be a

highly effective drug for refractory ventricular arrhythmias. The first case of suspected pulmonary toxicity due to amiodarone was reported in 1980.² Since then, there have been numerous case reports and at least two prospective evaluations.^{3,4} The incidence of pulmonary toxicity ranges from 5% to 17% depending on definition (the criteria used for the diagnosis of pulmonary toxicity vary from study to study) and length of follow-up.

The histology of amiodarone toxicity is a non-specific alveolitis. Large histiocytes with foamy cytoplasm containing lysosomal inclusion bodies are unique to patients receiving amiodarone. However, such histiocytes are seen in many patients taking amiodarone who do not exhibit clinical pulmonary toxicity. Such histiocytes may be only a “marker” of amiodarone administration rather than a sign of toxicity. The number of histiocytes is a reflection of the high concentration of amiodarone achieved in pulmonary tissue (severalfold higher than the serum drug level).⁵

The cause of pulmonary toxicity is unclear but is probably either due to direct drug toxicity or to a hypersensitivity reaction. The lysosomal inclusion bodies mentioned above are accumulated complexes of amiodarone and polar lipids. How these complexes adversely affect pulmonary physiology is unclear. A hypersensitivity reaction has been suggested by animal studies and by the findings of increased numbers of neutrophils and lymphocytes in

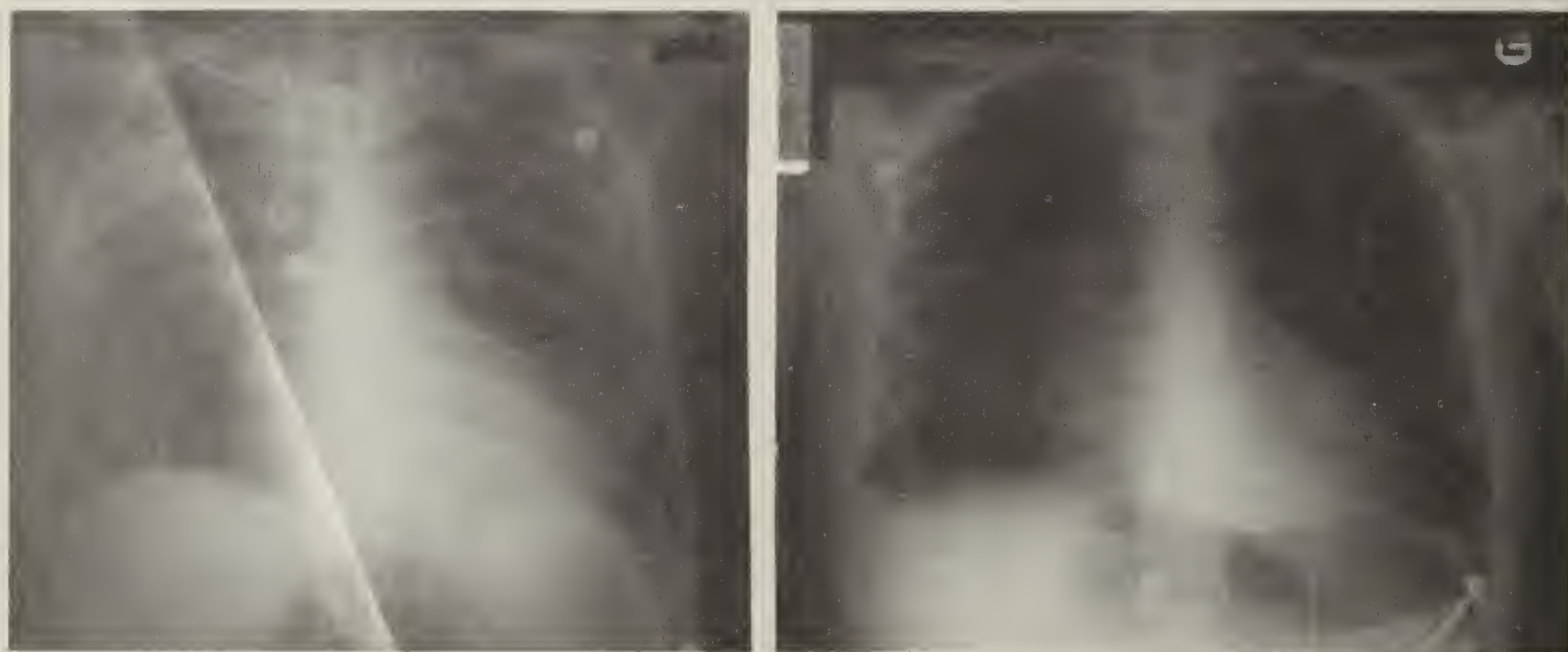


FIGURE 1. Chest radiograph obtained on the first day of pulmonary symptoms shows diffuse bilateral infiltrates. Right, Chest radiograph obtained seven days prior to symptoms demonstrates clear lung fields.

the bronchial alveolar lavage fluid of patients with amiodarone toxicity.^{1,5}

In previous reports, clinical pulmonary toxicity has presented as slowly progressive dyspnea, nonproductive cough, pleuritic chest pain, malaise, weight loss, and occasionally fever, usually occurring after at least three months of therapy. Chest radiographs demonstrate pulmonary edema or patchy infiltrates, usually in a peripheral location in the upper lobes.⁶ Pulmonary function tests show a restrictive pattern with a reduction in the diffusing capacity for CO.³ Most patients respond to discontinuation of amiodarone with or without concomitant administration of corticosteroids.

The two patients described in this report presented in a very different fashion. In both, acute severe respiratory insufficiency developed early in the course of amiodarone administration. Respiratory insufficiency necessitating intubation and mechanical ventilation developed over a brief period (<24 hours). As such, these two patients possibly represent a new and different form of amiodarone pulmonary toxicity or at least an extreme variation on those presented in previous reports. Only two previous reports suggest that amiodarone can cause acute or subacute pulmonary toxicity. Magro et al mentions that in three of 15 patients with pulmonary toxicity, it developed acutely within one month of beginning amiodarone. No details are provided.³ Wood et al reported two patients with probable pre-existing pulmonary toxicity in whom acute, fulminating irreversible respiratory failure developed after pulmonary angiography.⁷

Although the diagnosis of amiodarone-induced lung injury was not made by biopsy or autopsy in the two patients described here, a number of features suggest amiodarone to be the causal agent. Firstly, neither patient had respiratory problems prior to amiodarone administration. In addition, no recognized cause of acute respiratory failure was identified (ie, congestive heart failure, infections, trauma, aspiration, toxins, metabolic disorders, or pulmonary angiography, as in Wood's reported patients),⁷ and treatment to remedy such disorders, such as diuretics, inotropic drugs, antibiotics, and corticosteroids, failed to result in improvement. Finally, although bronchial alveolar lavage demonstrated foam-laden histiocytes, these may only be a marker of amiodarone administration—the combination of both increased cellularity and foam-laden histiocytes is certainly suggestive, if not diagnostic, of amiodarone-induced lung injury. These findings also raise the possibility that this acute syndrome is because of a hypersensitivity reaction.

In previous studies, pulmonary toxicity has been unusual in the first months of therapy, especially when the maintenance daily dosage of amiodarone is less than or equal to 400 mg.^{1,8} Both of these patients had less than two months of therapy on a daily maintenance dosage of 400 mg and would therefore be considered at low risk for the development of pulmonary toxicity. Both, however, received relatively large "loading dosages" (patient 1, 22.8 g over 25 days; patient 2, 18.2 g over 21 days). Such loading dosages have been reported to predispose pa-

tients to later pulmonary toxicity, although not the acute toxicity seen in these patients.¹

Neither of the patients described here survived in spite of withdrawal of amiodarone, steroid administration, and mechanical ventilation. Previous reports suggest that most patients with pulmonary toxicity will slowly improve (over months) after discontinuation of amiodarone. Although no controlled studies have been published, most authors believe that steroid administration may hasten improvement, but that it does not improve prognosis. Most but not all patients recover from the more chronic form of amiodarone pulmonary toxicity.^{1,8} Appropriate specific therapy for the acute toxicity described here has not yet been established.

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Esophageal candidiasis as a cause of esophagobronchial fistulas

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Acquired esophagobronchial fistulas in the adult are rare and are usually caused by malignancy or trauma. Rarely, such fistulas result from infectious causes. The consequences of esophagobronchial fistulas are serious and often fatal. We describe here a case of such a fistula occurring in a patient with esophageal candidiasis, with a fatal outcome.

CASE REPORT

An 80-year-old man was admitted to Brooklyn VA Medical Center with left lower lobe pneumonia. He had been well until two days prior to admission when he experienced sharp left-sided pleuritic chest pain, cough productive of yellow sputum, and a low-grade fever. He denied dysphagia, odynophagia, pyrosis, nausea or vomiting. He had no significant medical or surgical history. He had smoked two packs of cigarettes per day for 50 years. There was no history or clinical suspicion of any specific immune deficiency.

The physical examination revealed a cachectic man in no apparent distress. His blood pressure was 110/70 mm Hg; pulse, 88/min; respiratory rate, 20/min; and temperature, 38.4°C. Examination of the head and neck was unremarkable, and there was no evidence of oral thrush. Decreased breath sounds and crackles were heard at the base of the left lung. The rest of the examination revealed no abnormalities. A test for occult blood in the stool was negative.

The laboratory evaluation was remarkable for a white blood cell count of 24,000/mm³, with a differential count of 76% polymorphonuclear leukocytes, 8% band forms, and 16% lymphocytes. The hematocrit was 32%. Serum chemistry analysis was unremarkable. A chest film revealed a

large left lower lobe infiltrate and a large aortic aneurysm involving the entire descending thoracic aorta. A Gram's stain of the sputum was unsatisfactory. His arterial blood gas on room air showed a pH of 7.46, PCO₂ of 32 mm Hg, and PO₂ of 52 mm Hg. A computed tomographic scan of the chest revealed a dilated esophagus superior to the aneurysmal aorta (~5 cm in diameter) and compression of the left main bronchus by the aortic aneurysm.

On admission, a diagnosis of pneumonia was made, and therapy with penicillin, 600,000 units every six hours, and gentamicin, 60 mg every eight hours, was initiated. Although his chest pain resolved, he continued to have a low-grade fever. On the second day after admission, he complained of coughing up the food he had just eaten. However, his clinical status appeared to be stable, and the CXR, complete blood cell count, and arterial blood gas studies were not repeated. It was decided to observe and follow his clinical course. On the fourth day, he suffered cardiorespiratory arrest and expired.

At autopsy, the most significant finding was a 1-cm fistula between the left main bronchus and the adjacent esophagus (Fig 1). It was lined by a gray-white pseudomembrane composed of *Candida* budding yeasts, pseudomycelia, fibrin, and necrotic debris. The fungi infiltrated the deepest areas of the esophageal submucosa and the bronchial cartilage (Fig 2). Several ulcers were also noted adjacent to the fistulous tract and covered by a similar pseudomembrane. In nonulcerated areas, the fungi were focally associated with the superficial layers of the esophageal mucosa. Extensive bronchopneumonia with presence of vegetable fibers in the parenchyma confirmed a massive aspiration. Special stains for acid-fast bacilli were negative. The aorta was severely dilated and found to be atherosclerotic.

DISCUSSION

Esophagorespiratory fistula in the adult is rare and represents a serious problem. Most cases are caused by malignancies of the esophagus or the bronchus.¹ The remainder are caused

by trauma or infection. Cuffed endotracheal tubes that cause pressure necrosis of the membranous tracheal and adjacent esophageal walls, particularly against a rigid nasogastric tube, have been described as a relatively common traumatic cause.² In addition, during the performance of a tracheostomy, inadvertent perforation of the posterior tracheal and anterior esophageal walls may occur, leading to fistula formation.

Of the infectious etiologies, *Mycobacterium tuberculosis* has been described as the most common, followed by syphilis, histoplasmosis, and actinomycosis.³ It has been proposed that infection from tuberculosis and other granulomatous diseases causes enlargement of the paratracheal and other adjacent mediastinal nodes, resulting in caseation necrosis and subsequent abscess formation, erosion, and eventual rupture into the esophagus and the trachea.³

Esophagorespiratory fistulas may be present for weeks to years before the diagnosis is established. A fistula should be suspected if patients cough on swallowing liquids, especially when they are upright or on their sides (Ono's sign). Pulmonary rather than esophageal symptoms may dominate the clinical picture, with chronic cough, recurrent attacks of pneumonia, lung abscess, and bronchiectasis. Gastrointestinal symptoms include dysphagia, odynophagia, regurgitation, hematemesis, and abdominal distention caused by air entering the gastrointestinal tract on inspiration. Abdominal distension may be the only sign patients have on mechanical ventilation.

Esophageal candidiasis usually occurs in the immunocompromised host, especially in patients with acquired immunodeficiency syndrome (AIDS), hematologic malignancies, organ trans-

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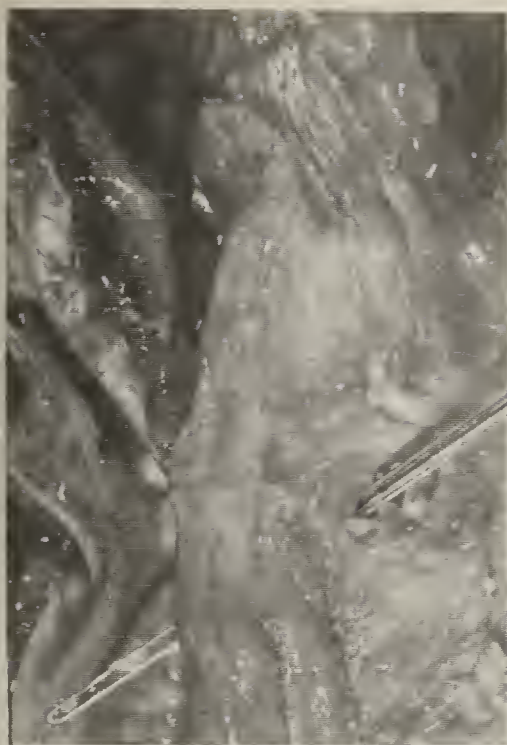


FIGURE 1. Esophagobronchial fistula. The probe runs through the fistulous tract between the esophagus (on the right) and the left mainstem bronchus.

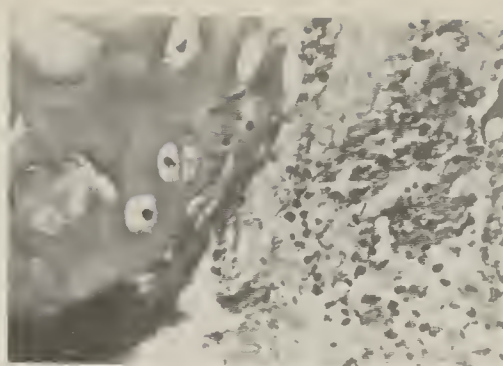


FIGURE 2. Invasive candidal infection. *Candida* (the black rounded yeasts) are seen infiltrating the bronchial cartilage. (periodic acid-Schiff stain; original magnification $\times 400$).

tion of the epithelium, associated with shallow ulcerations and pseudomembranes. Rarely, the organisms may invade the esophageal muscle layers and walls of the blood vessels, causing thrombosis, infarction, fibrosis, and disseminated infection. This invasive process by the candidal organisms may then lead to complications such as complete esophageal obstruction by a fungus ball, a localized structure of the esophagus,³ or a fistula to the lung leading to the development of an abscess.⁵

In reviewing the literature, we found only two cases of esophagobronchial fistulas, apparently attributable to infection with *Candida*. One involved a 36-year-old patient with AIDS,⁶ and the other was in a 22-year-old woman with leukemia.⁷ We postulate that the patient reported here developed stasis in the dilated midesophagus caused by physical compression from the enlarged aorta, leading to colonization and invasive infection of the esophageal wall by *Candida*. The blood supply to both the esophagus and airway

in this area is from vessels arising from the anterior surface of the descending aorta and could have been compromised by the aneurysm. Histologic examination of the autopsy material, however, showed no evidence of arterial insufficiency. At the point of crossing, the membranous posterior wall of the left mainstem bronchus directly abuts the anterior wall of the esophagus with no intervening serosa or fascial plane, thus providing no barrier to fistula formation.

Given the frequency of esophageal candidiasis in patients with AIDS and other immunosuppressed states, the possibility of esophagorespiratory fistula is increased in this population. As in this patient, the rapidity of the course and the fatal outcome highlight the importance of a greater awareness of the possible consequences of esophageal candidiasis. Emphasis on the early recognition and aggressive management of esophageal candidiasis should reduce such complications.

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Address correspondence to Editor, New York State Journal of Medicine, 420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication after editorial review. All letters are personally acknowledged by the Editor.

The "do-it-yourself" Heimlich maneuver

TO THE EDITOR: We wish to report a conversation recently in which several doctors were talking about the Heimlich maneuver.¹⁻⁴ One mentioned that he had performed it on his wife under dramatic circumstances, and fortunately it had worked well after the traditional slaps on the back had failed. He had practiced on a mannequin; therefore, he knew it took a great deal of force to perform the procedure successfully (having failed the first six practice times on the mannequin).

One of the other physicians recalled his personal experience and it, too, was quite dramatic. He was eating in the kitchen and had swallowed a piece of meat with a bay leaf on it. Suddenly, he realized that his air supply had been cut off. He could not breathe, could not speak, and made the usual *choking* signal to his wife, who did not understand him. Finally, he became dizzy and realized that he was about to pass out. He saw the rounded edge of the top of the kitchen chair, raced to it, and pushed as hard as he could in the

epigastric region; his own version of the Heimlich maneuver. Fortunately, the bay leaf floated out to the ground a couple of feet away, and he was able to breathe and quickly recovered.

We wish to remind readers that meat is not always the culprit. Salad dressing on lettuce or food is second in frequency, and many other objects as well may be aspirated. Pieces of hot dogs and candy, such as sour balls, are especially common causes in children.

About 3% of successful Heimlich maneuvers have been done by the victims on themselves. It may best be done by positioning one's fists above the navel and using several firm thrusts (repeated 2-6 times if necessary) directed upward to elevate the diaphragm, raise thoracic pressure, and thus produce expulsion of the foreign object. It can be done indirectly by using part of a chair or table (or other hard objects) to press upward in the area between the navel and sternum as was performed in the second instance mentioned here.

Henry Jay Heimlich, MD, reports⁵ that there have been over 20,000 successful procedures done in the United States in the past 15 years, and many others not reported. He is not aware of statistics in other parts of the world. Of the 3%³⁻⁵ that are labeled "do-it-yourself," he relates that the best way is to use your own fists with several hard upward thrusts. He recommends training in this technique for all physicians and emphasizes that considerable force is needed in performing these thrusts. Practice obviously helps.

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Paradigm of a profession under seige

TO THE EDITOR: We live in a society that is buffeted by uncertainty and challenged by forces often beyond its control. It fearfully faces some unpleasant choices and even more chilling consequences. Crashing about, not knowing which way to turn, it longs for someone to blame. The scapegoat must have stature. It has to be a role model whose values make it vulnerable. What better target than physicians? Their very paradigm makes them pregnable.

It has been said that we view ourselves as a profession that does things right and that we are guided by rigorous self discipline. Is this mantra the basis or our vision? If so, it is in danger of being destroyed unless we band together to protect the vitality and integrity of our profession. There is a fearsome cry, "Close ranks or die." We had better listen and ignore the seductive siren of whispers, murmurs, and shouts to go our own way. We can no longer afford to live in isolated splendor and hope to survive. It is still the same old story of divide and conquer and the hills are filled with hostiles. If we do not put aside our turf-guarding tendencies and our hidden agendas, we will eventually go the way of dinosaurs. This self absorption has often blinded us to the collective power we could exercise and left us weakened at critical moments.

A prominent, elected official commented on our potential to influence the electoral process. He felt that with our resources and those of our patients, we could make an incredible impact on the system. Without this



thrust, we have gone from being a protected species to becoming an endangered species.

In the process, one of the fastest growing indoor sports, Doctor Bashing, has sprung up. Seeking a new target, this once revered profession has become the victim. Admiration has been replaced by anger at the seeming affluence of physicians. Scant attention is given to our years of sacrifice.

The true irony is that those who throw the largest stones have no reluctance to scream for a doctor when an emergency confronts them. This love-envy relationship is further complicated by a never-ending stream of convoluted regulations and cost cutting measures. Physicians are expected to rise above all of this and to deliver errorless quality care. Often ignored is the failure of the system itself. Mistakes are unacceptable and are viewed as a fall from grace.

What is lost in this maelstrom of confusion, is the negative impact all this is having on the physician population. Future physicians are seeking other fields in ever increasing numbers, and many senior physicians are retiring early. We have a disturbing vision of a society waking up to find that physicians have become an extinct species. There will be recriminations, task forces, and crash programs. Unfortunately, all the kings men will have an exceedingly formidable task resurrecting "the lost profession."

What should we do to avert this doomsday scenario? Who do we turn to? What is our organizational response to all of this? How do we proceed in the midst of such turbulence? It is incumbent on us to support our leaders as they attempt to analyze our opportunities and threats.

One of our opportunities is to help our elected officials cope with the health care needs of patients at the inception of their plans. The threats are the budget deficits and society's seeming insensitivity to the victims of its neglect. At the same time, we seek to assess our strengths and our shortcomings. Our strengths are our clinical skills, compassion, and dedication. Our shortcomings are a perceived lack of social awareness and limited horizons.

We have to realize, furthermore, that payment of membership dues is only the beginning. We must become active participants in the process. We have to share our skills with our

communities by accepting voluntary positions in a host of community organizations and enterprises. We should surrender the mantle of the busy physician who only has time for his practice. Too many patients know the Wednesday syndrome of their physicians and the August departure of their psychiatrists.

The current business chant is "get closer to your customer," and in like fashion, we have to become more involved with our patients. For a start, let us listen to them.

What else must we do? As an organization that strives for excellence we need to consider a modified version of the seven categories of the Malcolm Baldrige National Quality Award.¹ They are the following: leadership, information and analysis, strategic quality planning, human resource utilization, quality assurance of services, quality results, and member satisfaction.

In this vein, we need to take a careful look at our organizations, starting with their internal operations and processes. How well are they functioning? Are they getting our message across? How effective are we as compared with organizations of similar size and complexity? Do we pursue the concept of continuous improvement in the quality of services we provide our members and our communities? How does the environment at large, view us?

In all of this, it is clear that we cannot continue to ask a handful of dedicated physicians to carry the whole load. We must all help. Seek out your legislators in their district offices. Let them know you care. Share with them your concerns for the health of their constituents and other pressing issues. Better than anyone else, physicians can teach others about health care. We do it all the time. Get to know your elected officials. Give them a chance to know and understand you.

The poetic plaint can be paraphrased to read as follows: "What a curious thing, to make us doctors and bid us sing!"²

Many of us thought that all we had to do was to be the best doctors we know how. We adopted the workaholic ethic and proceeded. We were ill prepared for the singing, but the time has come to learn new ways. We must then train tomorrow's leaders and help them to understand the moving target dynamics of an ever-changing world in which allies, neutrals, and

hostiles are interchangeable terms related to the issues at hand.

We did not come into medicine just for fame and fortune. Other fields could have been lucrative, but none more rewarding in the intangibles that make it all worthwhile. We entered medicine because of a passionate belief that to heal and comfort was the highest calling. We become a band of brothers and sisters bound by ties not of blood but of beliefs. We know who we are and what we are about. We have achieved much and there is more left to do. Let no one take this from us.

Fads are transient trends but beliefs such as ours, grounded in the bed rock of our humanitarian values and sustained by our compassion and commitment, must not perish. We have a cause. It is just. We will prevail.

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Physician recredentialing

TO THE EDITOR: The letter by Dr Alfred Gellhorn, Director of Medical Affairs, New York State Department of Health, and the reply by Dr Peter B. Farnsworth in the *Journal* addressed the subject of physician recredentialing.^{1,2} There are 67,000 physicians in New York State. The New York State Board of Regents disciplined 744 between 1983 and 1988.³ That is about 1.1%. Dr Gellhorn's solution to incompetence and negligence by 1.1% of our profession is to recredential everyone. Does the New York State Department of Health Department (DOH) hope to eliminate the bad doctors by recredentialing everyone expecting the bad doctors to fail? Dr Gellhorn's response is a bureaucratic one. What does it matter that it takes 99% of competent and non-negligent physicians away from taking care of people and money from other needed pro-

grams like maternal health? Is there evidence that forced examinations teach? Personally, I have always learned more from giving a lecture than listening to one and suspect the same principles apply to peer review as described.

Certainly, the bad doctors will not be improved by throwing examinations at them. If they can hire smart lawyers they can also hire smart tutors to pull them through peer review or written examinations. In my experience, a person who is unethical or immoral is unlikely to change. If they are incompetent and do not care, they are also unlikely to change. Bad people only understand economic deprivation as an incentive, and if forced out of medicine will be bad people in some other field.

From my experience in a referral practice for 27 years and from talking daily with physicians, I am convinced that even the least competent want to do a good job for their patients, and given the opportunity, they will. This raises the question of whether the adversarial attitude of the DOH helps or hinders the education of the 99% of physicians struggling to balance their time between obligations to patients, family, and study. I wonder if a thrust toward improved medical student selection, stronger educational incentives, and well-developed teaching aids would be better, abandoning all the rhetoric about "recredentialing" and "peer review." The data would not come out in the neat bundle Dr Gellhorn would like, and therein lies the problem. The DOH would have to really get down to work and gather information from the grass roots, like the Department of Agriculture does now, to identify progress. In other words, get out from behind an Albany desk and ask questions.

Recently, in the *New England Journal of Medicine*, there was a sharply

focused debate in the letters to the editor section on congenital syphilis.⁴ One comment impressed me. "First, in high-incidence areas, all mothers should be screened for syphilis at delivery." The author did not say all mothers should be screened, but rather recommended focusing efforts where the trouble lies. Transposed to the disease of medical negligence and incompetence, perhaps the DOH cannot identify the "high incidence areas." Perhaps the DOH knows the "high incidence areas" but has no "penicillin" for the illness. Perhaps the DOH has failed to convince the New York State Board of Regents and the legislature that it is thorough and fair, so that they will give it the powers needed to do the job.

Over five years ago, I suggested that the ophthalmology department at the hospital where I practice verify competency by regularly bringing in a reviewer from another city to spot check records. I also recommended that we reciprocate at the reviewer's institution to spread the cost. The idea was to rotate the reviewing task through the whole medical staff, so everyone would be involved, and learn. It was suggested that this be a by-laws-directed obligation for staff membership. However, the recommendation was not accepted. It is unfortunate we have lost the local control of this inspection of our efforts to an agency as politically motivated, remote, and impersonal as the DOH.

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In reply. I appreciate Dr Delaney's letter, in part, because it provides the opportunity to clarify one issue and, in part, because his recommendation for critical review of the ophthalmology department at his hospital is exactly what is being proposed as the major mechanism for recredentialing. Periodic physician recredentialing is not focused on the identification of the fraudulent or the grossly negligent doctors. Other mechanisms are in place as Dr Delaney has noted. Most physicians in practice recognize that there is always room for improvement in their medical knowledge and skills. This is why, at the national level, there is a major emphasis on the development of practice guidelines that will be used for evaluations and will be modified as data on outcomes are accumulated. As Dr Delaney proposed for his hospital, the major recredentialing mechanism proposed in New York would be peer review of physicians' practices to determine compliance with guidelines developed by their own specialty organization. A written examination would only be required for those physicians who are no longer seeing patients but still wish to hold a current medical license in New York.

In spite of the animus that Dr Delaney holds for DOH bureaucracy, it is to be emphasized that the recredentialing proposal explicitly involves fellow physicians and professional peers to carry out this process, not DOH personnel. The question is whether or not the medical profession will accept the challenge.

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Under the Safety Net. The Health and Social Welfare of the Homeless in the United States. Edited by Philip W. Brickner, MD; Linda Keen Scharer, MUP; Barbara A. Conanan, RN, MS; Marianne Savarese, RN, BSN; Brian C. Scanlan, MD. New York, WW Norton & Co, 1990. \$27.95 (hardcover)

Homelessness—1984. Not understood, not wanted: A problem not solved by Reagan's safety net—that gossamer veil of superficial intent. *Homelessness—1991.* The continuing presence of social failure amidst 20th century affluence.

This book describes the remarkable success of a national health care program for the homeless. It is both a chronicle, a treatise, and a much needed text. Although the seriousness and magnitude of homelessness in America may be even greater in 1991 than in 1985, Brickner and his coeditors have developed services, tested them, and now report on their experience in meeting the health care and social welfare needs of the homeless in America. Their work constitutes a truly extraordinary accomplishment.

An epidemic of homelessness arose in the 1970s and early 1980s. By 1985, homeless people were sleeping in the streets and parks of all major American cities, in abandoned buildings, and single-room occupancy (SROs) hotels.

The national Health Care for the Homeless Project was constituted by three coalitions in 1985. A partnership was developed by the Robert Wood Johnson Foundation, the Pew Memorial Trust, and the United States Conference of Mayors to support this project.

Community coalitions in the 50 largest cities composed of social and medical agencies submitted competitive grant proposals to develop health care services for the homeless. Nineteen cities were chosen to participate in the national project.

Interdisciplinary teams of health care providers were established in each of the 19 cities to deliver services to homeless men, women, children, and families in communities, shelters, clinics, and hospitals.

In 1985, there were no experts, and there were essentially no data or literature on serving the homeless. The 109 contributing authors who have written the 26 chapters of this book have masterfully filled this void. The editors Brickner, Scharer, Conanan, Savarese, and Scanlan have worked together as a team in the Department of Community Medicine at St. Vincent's Hospital in New York City since 1974. Their early description of serving homebound elderly and homeless men living in SROs are seminal publications in the field of medical care.

Philip W. Brickner was the Director of the National Health Care for the Homeless Program. He and his staff made repeated visits to each of the 19 programs during the four years of the project. Helping to solve problems, to share experiences, and to speed the process of development, they created a national cadre of experienced professionals dedicated to providing health care for the homeless. The 109 contributors are drawn largely from this cadre.

Under the Safety Net is an authoritative work that reflects the problems of the homeless throughout the United States. Homeless people—women, men, and most poignantly, the street kids—have also authored this book. In almost every chapter, vignettes, stories, poems, and songs

by or about homeless people keep the reader honest and connected with the realities of this social tragedy.

Under the Safety Net is a shocking and sobering story. "A searing call to action for every citizen . . ." noted the books previewers. The book is organized into three parts: "The Challenge," "Clinical Concerns," and "Programs and Partnerships."

THE CHALLENGE

The challenge of homelessness, its origin, and causes are described in the first five chapters. The evolution of homelessness is aptly described by Max Michael in his chapter entitled "Slouching Toward Chaos: American Health Policy and the Homeless." The demographics of the homeless are described: who are they and where do they come from. The numbing answers to these questions in essentially all cities are that they come from us, from here, and usually not from somewhere else. The new homeless, youth, women, and homeless families are also described. The latter are the fastest growing subset of the homeless population, exceeding 50% of the homeless in some cities.

The planning and organizing of the national program are described in the first five chapters. In each city, the project was designed to meet local needs, to include many if not all of the concerned agencies, provide care, and build networks of service providers to serve the many needs of the homeless persons and families.

CLINICAL CONCERNS

The clinical needs of the homeless are described in the 11 chapters of the second part of this book. Initial chapters describe outreach, communication, and the establishment of continuing relationships. The special needs of particularly vulnerable groups are then described. In the chapter entitled "Health Care for Familyless, Runaway Street Kids," often called throwaways, the staggering losses that this epidemic of homelessness is wreaking on our children are laid out, directly and inescapably. The authors point out that "street kids are not emancipated youth, they are abandoned children."

The special health concerns for women, the elderly, the disabled, and the mentally ill are described. For each group, there are a special set of medical risks including heat and cold, the extremes of the environment, poor nutrition, alcoholism and other substance abuse, violence, and sexual abuse. Tuberculosis, AIDS, hypertension, and depression affect large numbers of the homeless. The prevalence data on epidemic tuberculosis and AIDS among the homeless are frightening.

The authors present strategies that have been found to be effective for treating these conditions in the 19 cities. Approaches and programs for treatment are described for tuberculosis, AIDS, hypertension, mental illness, and substance abuse. A unique contribution of this national program was the establishment of hospices to provide supportive medical care at a less intensive level than hospital care and at much reduced cost.

Hospices for the homeless have become important resources in most of the 19 cities. After recovering, patients are often discharged from a hospice into housing rather than to the streets. The interconnectedness of the realities of homelessness and the medical problems of the homeless is stressed throughout this section.

PROGRAMS AND PARTNERSHIPS

In the first seven chapters, the authors lay out the organizational framework of successful health care for the homeless programs. Successful outcomes in these programs required more than the conscientious delivery of medical care. They were dependent most of all on the initiation of change within the complex network of services and agencies responsible for coping with the homeless. Success ultimately depended on the capacity of the governing board of each coalition to assess needs and functions objectively; set goals and objectives; and establish policies, guidelines, and limits. Boards sponsored the programs of the project and were legally accountable for them.

Staff development was essential for each project. Development included training, sustenance, and preventive strategies to avoid staff burn-out, the exhaustion from the constant stress that surrounds the condition of homelessness.

Case management, not medical care, is what is needed to overcome homelessness itself. Each project developed case management to provide support, asylum, rehabilitation, and a permanent living place to homeless individuals and families. Specific examples are given to document each of the components of staff development, case management, and the securing of benefits to which the homeless are entitled. Outreach is the first component of a health care program for the homeless. It is the capacity to engage homeless individuals and families actively in the process of solving their own problems that is the basic challenge for workers in this field.

In the final four chapters of the book, the nature of public and private partnerships that have led to building a successful coalition are described. The 20-year history of the program at St Vincent's Hospital documents a successful three-tiered approach to the care of homeless individuals. The tiers include community outreach in the streets, health services in shelters, and medical care in hospital clinics. Chapters on the education of medical students and nurses in the special health and social needs of homeless describe the educational programs stimulated by this program.

In summary, this book provides a wealth of information on the care of the homeless in the United States. It

covers an extensive range of experience and information. The text is written accurately and clearly. Because the problems of homeless individuals are all closely interconnected, there is some repetition among the various chapters. The editors have done a masterful job, however, in providing a uniformity of approach and continuity of style.

The objectives that the authors have set out have been achieved. This book describes the creation of an effective Health Care for the Homeless Program in 19 cities. This experience is chronicled from original concepts to well-established model programs. The text combines traditional medical care with the equally essential interventions of social welfare, case management, outreach, hospice care, and counselling.

The project was originally financed through the collaboration of the Robert Wood Johnson Foundation and the Pew Memorial Trust. During the course of establishing individual projects, local and state funds were obtained. National philanthropic activity was developed simultaneously by Comic Relief, which raised public awareness and donated large amounts of money to the Health Care for the Homeless Project, and finally, the Stewart B. McKinney Homeless Assistance Act was passed by Congress and signed into law by President Reagan in July 1987. The Act was a response to the growing problems of homelessness in the United States. It was catalyzed by the National Health Care for the Homeless Project and continues to support health care for the homeless throughout the United States.

The National Health Care for the Homeless Project serves as an important milestone in health services delivery in the United States. Much as the polio epidemic of the 1950s forced the restructuring of health departments and public health services throughout the nation, much the same way Smallpox Eradication Program forced a restructuring of public health services and health education in many countries throughout the world, the National Health Care for the Homeless Project stands as a model for addressing serious national medical and social welfare problems. It offers an approach that can be used to overcome substance abuse, interpersonal violence, and chronic mental illness, to name a few. The book is a highly educational and much needed chronicle, treatise, and text. The authors and foundations are to be congratulated.

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New York State Department of Health: HIV seroprevalence studies

The following article is the first in a two-part series condensing information from the May 1991 supplement to the American Journal of Public Health, New York State HIV Seroprevalence Project, which summarizes the results of these efforts in New York State.

In June 1987, New York State embarked on an extensive effort to determine the prevalence, distribution, and trends of human immunodeficiency virus (HIV) infection in the population. Information was needed to assess and combat this priority health problem. Statewide serosurveillance for antibody to HIV was performed using blind testing of available blood samples. Initially, six subpopulations were selected as "windows" to view the epidemic (newborn, homeless adolescents, prisoners, and clients of family planning, sexually transmitted disease, and drug treatment clinics).

Impetus for Statewide HIV Serosurveillance

Whereas AIDS case report data had been invaluable in plotting the increase in the number of individuals affected with AIDS and delineating risk factors associated with this occurrence, severe deficits in understanding the epidemic remained, impeding public health interventions. Of importance, the current distribution of this infection could not be determined from examination of case reports. The HIV spectrum extends from individuals with asymptomatic HIV infections to those with AIDS. The major portion of this spectrum, asymptomatics, is not likely to be reported. To determine occurrence of infection, direct and contemporary measures of those infected needed to be employed. HIV serosurveillance provides a measure of those currently infected.

A monitoring system based on a representative and continuing serosurvey was needed to track the progress of the epidemic. In addition to overall statewide trends, the primary monitoring for the epidemic would be the collection of information on changes over time for age and racial/ethnic groups on a statewide, regional, and community basis. Data from AIDS case reports are not as suitable for monitoring purposes because of the lag time between infection and AIDS.

The method selected by the Department of Health was a seroprevalence survey relying on blind testing of

available blood specimens for determinations of antibody to HIV. This method was selected as a feasible approach that could be implemented quickly without the costs associated with a community household survey. The potential problems of self-selection and bias were associated with nonblind community surveys that require voluntary participation and consent. Blind seroprevalence studies, of the type employed in New York State, have the advantage of being able to use available blood specimens, minimizing cost and maximizing participation. Informed consent is not part of the process.

The childbearing population is particularly important in efforts to monitor the HIV epidemic. Women of childbearing age are a key group with respect to their exposure to the virus, their susceptibility to infection and their involvement with perinatal transmission. Intravenous drug use (IVDU) is now the leading risk factor associated with AIDS. Infection levels in women are directly related both to their own IV drug use and through heterosexual transmission, which to this point has included mostly drug-using males. Women may also acquire infection from gay or bisexual sex partners.

As the epidemic increases, particularly for intravenous drug-using males, it can be expected that monitoring the level of infection through newborn seroprevalence will detect variations of this problem in childbearing women that have been influenced by changes in prevalence in the IVDU population.

Newborn HIV Seroprevalence

In November 1987, the Department of Health initiated the newborn study to document the extent of HIV infection in childbearing women. Since mandatory blood specimens are obtained on all newborns in the state for the detection of metabolic disorders and the presence of antibody in the newborn is indicative of infection in the mother, these specimens were utilized to test for antibody to HIV. The presence of antibody does not necessarily indicate infection of the child. Only a proportion (30%–50%) of seropositive newborns will be infected. Applying these proportions to the number of seropositive newborns can yield estimates of the number of children born with HIV infection.

The following objectives were established for the newborn study: (1) to establish the baseline prevalence of infection in this population, (2) to monitor trends in infection over time, (3) to determine the geographic distribution of infection, (4) to monitor trends of infection in various subpopulations (racial/ethnic groups), and (5) to use the information to target preventive activities.

As of March 31, 1990, a total of 653,328 blood specimens were analyzed for HIV serologic status. The overall seroprevalence rate was 0.66 %: 1.24 % in New York City (NYC) and 0.17 % in the rest of the State (Table 1).

Of the 170 zip codes in New York City with 100 or more births, 31 (18.2%) had HIV seropositivity rates in

TABLE I. Percentage of HIV Positive Newborns by Region for New York State, November 30, 1987–March 31, 1990

Region	Number Positive	Total Tested	Percentage Positive
New York State			
Exclusive of New York City	801	346,522	0.17
NYC Suburban	329	120,423	0.27
Mid-Hudson Valley	71	29,450	0.24
Upstate Urban	119	88,088	0.14
Upstate Rural	82	108,583	0.08
New York City	3,850	294,062	1.24
Manhattan	799	50,364	1.58
Bronx	885	58,003	1.72
Brooklyn	1,352	104,512	1.29
Queens	424	87,474	0.63
Staten Island	77	13,000	0.57

excess of 2% and 13 (7.6%) had rates in excess of 3%. HIV seroprevalence rates for racial/ethnic subgroups showed black infants with a rate of 2.19%, Hispanics 1.43%, whites 0.34%, and other newborns 0.27%. An increase in seroprevalence with increasing maternal age was seen for blacks and Hispanics but not for whites or other races. The seroprevalence rate peaked for black and Hispanic infants born to women in the 30–34 year age group. The seroprevalence rates increased from 0.16% (1 in 624) for 14-year-olds to 1.41% (1 in 71) for 24-year-olds, a ninefold rise.

Black infants had an HIV seropositivity rate of 0.95% outside New York City, followed by 0.61% for Hispanic newborns, 0.06% for whites, and 0.19% for other races. Whereas only 14.0% of the newborns tested were black or Hispanic, 69.4% of HIV-seropositives were either black or Hispanic. For black newborns, the HIV-seropositivity rate increased with maternal age, peaking in the 35+ age group.

Monitoring Newborn Seroprevalence Trends

A major purpose of the Newborn HIV Seroprevalence Study is to monitor HIV infection in childbearing women with particular attention to specific geographic, age, and racial subgroups. Because of the ongoing nature of the study, the findings can be used to identify trends or changes in trend of HIV seroprevalence over time in various subgroups of childbearing women, a representative group of the overall population of women of childbearing age.

A trend analysis was conducted on the first 27 months of data, from December 1987 through March 1990, in specific subgroups of age, race, and geography. Determinations of a change in the level of HIV infection in a given time period is of paramount importance in determining the severity of the HIV problem and the need for preventive efforts. HIV seroprevalence determinations over time yield both current and secular estimates of infection. When plotted for the 27-month period, HIV infection in childbearing women both in New York City and New York State excluding New York City showed no trend. In New York City, all but one age/racial subgroup demonstrated no statistical evidence of a

trend; a statistically significant negative trend was seen for New York City women less than 20 years of age. In New York State exclusive of New York City, the rate increased slightly for women 20–29-years old.

Estimating Bias in the Newborn Seroprevalence Study

A major concern in the newborn seroprevalence study focused on the completeness and representativeness of the data. It was necessary to evaluate the extent to which the serosurvey captures the population of interest. This evaluation of completeness and representativeness had three components: (1) to provide an estimate of the number of samples never received by the Newborn Screening Program; (2) to enumerate the specimens received by newborn screening that were invalid or unsuitable for any testing and for which a repeat specimen could not be obtained; and (3) to enumerate the specimens that were insufficient or unsuitable for HIV testing after the newborn screening was completed. Data obtained from the three components were useful in assessing potential bias in the newborn study.

The evaluation of completeness and representativeness revealed that specimens from an estimated 1.5% of infants born to New York State residents were not received and 3.7% of the 286,150 newborns eligible for testing were not tested. In addition, the analysis showed that 54% of untested specimens were from New York City, while only 45% of the tested specimens were from New York City. There was a higher percentage of untested newborns with an unknown or out-of-state residence. In both New York City and New York State exclusive of New York City, the untested group had a higher percentage of blacks. Untested specimens represented a disproportionate share of lower birthweight infants (<2,500 g) than total specimens received.

Assuming the seroprevalence rates for the 1.5% of missing specimens would be equal to those observed for their racial/ethnic and geographic subgroup and including those additional potentially seropositive infants to state seroprevalence rate calculations would increase the overall rate from 0.642% to 0.647%. In addition, assuming all of the estimated 10,520 untested to be seropositive and including these infants in the rates calculation would increase the overall seroprevalence rate nearly sevenfold, from 0.64% to 4.29%.

Comparing Newborn Seroprevalence Data to Hospital Discharge Data

This study was initiated to estimate the proportion of HIV-seropositive newborns who are hospitalized for an AIDS-related diagnosis (ARD) within 12 months of birth and to characterize the hospitalizations of these infants. Information from the first hospitalization of a case was used in the analysis.

From December 1987 through June 1988, 995 HIV-seropositive newborns were delivered. Of the infants born during this same period, 151 were hospitalized with an ARD within 12 months of birth; assuming all infants in the hospitalized set were members of the HIV seropositive set, 15% of HIV-seropositive infants born in these seven months were hospitalized with an ARD

within 12 months of birth. Assuming maternal transmission rates of 25%–60%, an estimated 250–498 of the 995 HIV-positive newborns were actually HIV-infected.

There were a total of 240 hospitalizations for the 151 ARD cases during the 12 months of follow-up. Seventy-three percent had only one hospitalization during the 12 months. These accounted for a total of 5,772 patient days ranging from 1 to 368 days per hospitalization. Nearly half of the hospitalizations had a length of stay exceeding 10 days. Over one quarter of the cases were first hospitalized within 90 days of birth. More than half the cases were first hospitalized within six months of birth.

Summary

In the next issue of *Epidemiology Notes* a summary of articles related to HIV seroprevalence in female prisoners, clients of family planning clinics and runaway and homeless adolescents will be presented. In addition, the analysis of geographic and sociodemographic factors in newborn HIV seroprevalence, projections of AIDS incidence in women, and a summary of the AIDS epidemic in New York State will be included.

Protocol for HIV testing of newborn blood specimens

The protocol for HIV testing of newborn blood specimens has been described in detail by Novick et al.¹ Briefly, a dried-blood specimen is obtained from each infant along with certain demographic information, including the mother's age, zip code and county of residence, the newborn's race/ethnicity, and the month and year of birth. Hospitals are informed of the need for accurate, complete reporting and are contacted, if necessary, to obtain missing information. For the HIV study, the demographic information—but not identifying information—is entered into a separate, unlinked data base, where each record is identified by a unique, randomly generated number. The same number is assigned to a portion of the blood specimen. All metabolic disorder screening tests are completed before specimens are submitted for HIV testing.

Insufficient or unsuitable blood specimens left over after the metabolic disorder screening are excluded from the blinded HIV seroprevalence study. The number of these specimens is carefully tracked. Repeat specimens cannot be obtained at this stage because the blinding process makes it impossible to link the identity of the infant to the specimen. To ensure that only one specimen representing each childbearing woman is tested, all specimens except one from a multiple birth event and all repeat specimens requested for follow-up by the Newborn Screening Program are excluded.

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Swimmer's itch—Schistosome cercarial dermatitis

The larvae of certain blood flukes of birds and mammals may penetrate the human skin and cause a dermatitis, sometimes known as "swimmer's itch." Such infections may be prevalent during the swimming season among bathers in inland fresh water lakes. Outbreaks of swimmer's itch, or schistosome dermatitis, are reported from various areas in New York State on an annual basis. The dermatitis results from swimming or wading in schistosome-infested ponds or lakes where a very complex life cycle exists.

In New York State, and most other states, various aquatic bird species are the primary definitive host for several schistosome (flake) species. These fluke species do not mature in man and do not cause the classical human schistosomiasis seen in Africa, Asia, or South America. The lesion seen in cases of swimmer's itch manifests itself as scattered papules, each papule representing the site of penetration of the skin by a schistosome cercaria.

Cercariae are free-swimming larval worms produced in the tissues of certain snails and shed from the snails during favorable environmental conditions. Normally, one snail can produce thousands of cercariae. The cercariae penetrate the skin of birds and develop into adult worms. Feces of these infected birds contain the schistosome eggs, which will hatch into the miracidium stage when the eggs contact water. The miracidia are attracted to chemicals emanating from their snail hosts and penetrate the snail to develop into the cercariae.

This general life cycle is closely associated with the local environmental and faunal conditions existing at any particular pond or lake. The warming of water at the shore areas stimulates both the movement of snails toward the warmer water and the emergence of cercariae from the infected snails. Cases of human cercarial dermatitis will generally have been exposed at bathing areas around these infested waters.

Cases of schistosome dermatitis are generally reported in children or adults during May, June, and July. Cercariae penetrate the skin of humans as the water on the skin evaporates. Thus, children or adults who wade in the water and subsequently walk along the shore or play in the sand and do not towel dry themselves run a higher risk of cercarial penetration than those who dry themselves after swimming. Quite often, the skin area under bathing suits may be affected with these lesions when the skin and suit are wet and dry slowly.

The cercaria has a head capsule with two oral suckers and a bifurcated tail. On penetration, the tail is shed and the anterior oral sucker aids in the short intradermal migration until the host's immune response attacks the invading parasite, resulting in a lesion not unlike a mosquito-bite in appearance and sensation. A victim's first exposure to infested water may result in an asymptomatic condition. Repeated exposure increases the victim's sensitization to the foreign protein of the schistosome head capsule and produces a generalized

rash whenever exposure to water, evaporation of water, and penetration of cercariae occurred. Exposure in heavily infested water can result in a serious pruritic rash.

The typical lesion manifests itself as scattered papules marking the point of entry of the cercariae. The clinical picture depends on the degree of hypersensitivity induced by previous exposures. The reaction consists of an initial tingling sensation (within minutes) lasting for about one hour and is then accompanied by a macular eruption. There may be diffuse erythema or urticaria during this phase. The initial itching usually subsides for a quiescent period of 10–15 hours. The quiescent period is followed by a maculopapular and urticarial eruption with intense itching. This delayed reaction generally resolves within a week. These cercariae do not penetrate beyond the skin in humans.

Although the disease is self-limited (because of immune responses) and does not represent a threat to human life, it represents a nuisance with obvious implications for many recreational activities around many fresh water lakes and ponds in New York. Treatment is based on the symptoms presented by the infected patient. Antihistamines are often useful in relieving primary symptoms associated with the condition. For further information, please contact the Bureau of Communicable Disease Control at (518) 473-4436.

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HIV guidelines for health care workers

The Centers for Disease Control (CDC) issued guideline recommendations for HIV-infected health care workers on July 12, 1991. These guidelines are similar to the New York State Department of Health recommendations of January 1991 that call for voluntary HIV testing, reliance on universal infection control procedures and case-by-case evaluation of infected workers involved in certain invasive procedures. The CDC recommends that “exposure-prone” procedures be identified for special attention. The New York State Department of Health is working with specialty groups and health care organizations to develop a consensus list of “exposure-prone” procedures to be applicable statewide.

BOOK REVIEWS

BLACK WOMEN IN WHITE: RACIAL CONFLICT AND COOPERATION IN THE NURSING PROFESSION, 1890-1950

By Darlene Clark Hine. 228 pp, illustrated. Bloomington, IN, Indiana University Press, 1989. \$35.00 (soft-cover)

Just when we feel that we have grasped a fairly broad historical perspective, along comes a book such as this one to remind us of our blindness as to time, place, and people. This is a carefully documented study of racial conflict and cooperation in the nursing profession from 1890-1950. The author vividly describes the struggles of black women nurses, "a triple index of inferiority." One sentence strikes a resonant chord in the psyche of those who did their residencies before the Bell Commission report: "The political economy of the hospital depended upon a constant supply of obedient, disciplined and inexpensive workers willing to provide up to 70 hours a week of unremitting labor."

The author analyzes the origins of the Black hospital and nurse training school movement in both the North and the South, as well as Black collegiate nursing education. She looks at racism, status, and professionalization as it affected them and the unique organizations that they designed and developed. She describes the integration of nursing after World War II when the outcasts could finally come in the front door.

This slice of history is even more telling as we confront the shortage of nurses, which is having so heavy an impact on the current health care system. Nowhere is this more evident than in the underserved segments of our society. It is against this background that we stand in awe of these unforgettable portraits of women who surmounted incredible obstacles to bring health care to their communities.

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ANESTHESIA FOR CARDIAC SURGERY

By James A. DiNardo, MD, and Michael J. Schwartz, MD. 237 pp, illustrated. East Norwalk, CT, Appleton & Lange, 1990. \$55.00 (hardcover)

The authors' stated goal in writing this book is to "provide the background information and approach necessary for the sophisticated, informed evaluation of patients undergoing cardiac surgery." The book is quite comprehensive and easily readable. Most chapters are well organized with the same pattern following throughout the book. In addition, the book is well presented with many useful graphs, charts, and line drawings.

Conceptually, the book is divided into three areas. The first introductory area includes chapters on preoperative assessment, cardiac catheterization, and monitoring. The second area deals with specific disease states and specific procedures including chapters on myocardial revascularization, valvular surgery, congenital heart disease, pericardial disease, and emergency cardiac surgery. The last part of the book deals with more general topics of cardiac surgery including cardiopulmonary bypass, myocardial preservation, central nervous system injury, and postoperative care.

Perhaps the weakest part of the book is in the first few chapters, which is a shame, since this serves as an introduction to the book for most readers. Although the chapter on cardiac catheterization is well presented and complete, the chapters on preoperative assessment and monitoring have multiple short comings. I found the chapter on preoperative assessment to be very superficial and in some specific cases outdated. The chapter on monitoring is also somewhat outdated and incomplete. The author spends a lot of time discussing relatively old information (eg, CVP, arterial line, pulmonary artery catheterization) and relatively little time on some of the new monitoring modalities (eg, transesophageal echocardiography, right ventricular ejection fraction, noninvasive continuous cardiac output modalities). In addition, chapter 11 discusses in depth neurologic injury associated with cardiac surgery, the topic of central nervous system

monitoring should have been included in the chapter dealing primarily with monitoring.

The second part of the book dealing with the specific disease states is for the most part up-to-date, complete, and easily readable. These chapters are very well organized, with appropriate discussions of physiology, epidemiology, and anesthetic management. The areas dealing with specific anesthetic management are particularly well organized with discussions with goals, preinduction, induction and post-induction management.

The last part of the book is also well presented. The chapters on cardiopulmonary bypass and myocardial preservation provide a clear, concise conceptual, and practical approach. In contrast with the first chapter of the book, the chapter on neurological injury is comprehensive and complete, yet easily readable. The last chapter dealing with postoperative care is somewhat generalized but probably should be so in the context of this book.

This book is quite competitive and perhaps more reader friendly compared with other books in this field. For the most part it achieves the authors' stated objectives. Once readers get through the first few chapters, they will find it informative, enjoyable, and easy to read.

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CURRENT PRACTICE OF CLINICAL ELECTROENCEPHALOGRAPHY.

Second Edition. Edited by David D. Daly, MD, and Timothy A. Pedley, MD. 844 pp, illustrated. New York, Raven Press, 1990. \$85.00 (hardcover)

Although described as the second edition of a book with the same title published in 1979, this is really a new book. The first edition was a collection of lectures given at annual courses on electroencephalography (EEG) and only dealt with selected topics. The second edition is a complete text in the

field of clinical electrophysiology of the brain, as practiced at some of the best medical centers in the United States. The editors have been remarkably successful in assembling a distinguished group of authors, who are all practitioners, teachers, and investigators in their fields, to write a text specifically directed toward neurology residents/fellows in training and the neurologist in practice. It is larger and more comprehensive than any of the other books used by residents at present, and yet it does not presume any previous knowledge in the field. The initial chapters describe the basics of instrumentation and the basic neurophysiology of brain electrical activity, followed by the normal and abnormal EEG. Long-term monitoring and depth electrode studies in suspected seizure disorders are adequately described, and there are succinct chapters on evoked potentials and the laboratory study of sleep disorders. The application of evoked potentials in the diagnosis of multiple sclerosis is well summarized in a separate chapter, and finally there is a very good description of the present practice of intra-operative monitoring by the group of electrophysiologists at the Mayo Clinic. Magnetic brain stimulation is not yet in clinical use in this country outside of a few specialized centers, and hence it is not discussed.

The authors have all maintained a very high standard of accuracy, completeness, and relevance in writing their chapters. Recent work and the present consensus have been incorporated; the references in most chapters span the time period up to 1989. There are plenty of illustrations, all of good quality. I wish that there were more tables to summarize facts in some of the chapters since these are invaluable in the learning experience. The editing has been carefully done, and there is an evenness of content and presentation from chapter to chapter. Very little repetition is noted except when it is advantageous to do so. The views expressed represent the mainstream in the practice of EEG in North America and the role of clinical brain electrophysiology in the era of advanced brain imaging has been evaluated fairly. An understanding of computer techniques as applied to improved analysis and display of electrophysiologic data will be increasingly important, and Dr J. Gottman of Montreal provides a very clear introduction to the subject. Topographic

brain mapping is not dealt with in detail, presumably because its clinical validity and usefulness is still not established. The emphasis throughout the book has been on the roles that electrophysiologic techniques are likely to play in the next decade of neurologic practice, and the book aptly concludes with a few speculative comments by the authors on the future.

Dr John Knott, the doyen of electroencephalographers in this country, has written a fine introduction to the book. It must be read by all who intend to use the book seriously. He explains the organization of the chapters, and suggests variations in the order of study depending on the previous knowledge, experience, and the aims of the reader. For instance, the resident starting his training would probably begin with chapter 6, the normal EEG in the adult and child, and leave out the initial chapters on instrumentation and neurophysiology to a later date. Similarly, chapter 7 on the EEG of the newborn can best be deferred until the reader is quite familiar with the adult EEG and has started to look at recordings of babies. Chapters 16 to 23 on evoked potentials, sleep, and electrophysiologic monitoring could each be read separately as the resident is introduced to these topics. As Dr Knott points out, the subject cannot be learned in the library. This text can only be used effectively as part of a proper teaching program that includes introductory lectures, continued reading of records under supervision, and a brief period in the recording laboratory. I can think of no better book if used in this way.

There are only two criticisms of this otherwise excellent book. A description of normal EEG patterns in the adult is the most likely starting point for the trainee, perhaps preceded by the chapter on electrical fields and recording techniques. Hence, chapter 6 should have started with a review of the basic organization of brain electrical activity as seen in a recording, with a description of wave forms and their terminology. The detailed account that follows would then be more intelligible to the novice. The variations of the EEG in childhood and in old age from the normal adult pattern have been incorporated into the general description of each rhythm. This would be difficult for a beginner to remember and use when interpreting an EEG on patients at the two outer

age limits. The normal maturation of the EEG from age 1 to 25 years and changes in senescence could have been described separately after the account of the normal adult EEG. A mental picture of the normal EEG at any specific age, and its acceptable range of variation, are essential for the proper evaluation of a record.

The EEG abnormalities in head injuries of varying degrees merit a short chapter of their own. Severe head trauma resulting in unconsciousness is discussed in the comprehensive chapter on coma, but the EEG abnormalities in lesser degrees of brain injury and their significance are not described. The EEG can be useful in the prognosis and follow-up of head trauma patients and may be the subject of expert evidence in medico-legal circumstances. The electroencephalographer should have a good knowledge of the value and limitations of the EEG in the management of such patients.

This book bridges the gap between the small introductory texts, such as the *Primer* by Spehlmann, and the advanced reference text by Niedermeyer and Lopes da Silva. It has the great advantage that it can be used both as a guide by the beginner enrolled in a supervised clinical teaching program, and as a reference text for daily use by the practicing clinical electroencephalographer. No other book would probably be necessary in clinical practice for the next few years.

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MANUAL OF GYNECOLOGIC ONCOLOGY AND GYNECOLOGY

Edited by M. Steven Piver, MD. 416 pp, illustrated. Boston, MA, Little Brown & Co, 1989. \$22.50 (spiralbound)

This manual is a comprehensive outline of a variety of oncologic and benign gynecologic disorders. As editor, Dr Piver has gathered a panoply of authors who are experts within their respective fields of interest. Aimed at the medical student/resident/fellow, the manual is actually two manuals. Part I primarily deals with oncology and contains chapters addressing malignancies either by cell type or site of

origin. Particular emphasis is given to ovarian malignancies, followed by cervical, endometrial, myometrial, and vulvar malignancies, with lesser discussions of the rarer gynecologic malignancies. The etiologic risk factors, signs and symptoms, pathology, staging with pertinent workup, treatment, and prognoses are described in outline form. Of note are several chapters relating to the principles of adjunctive care, specifically, chemotherapy and radiation therapy. These chapters provide a basic understanding of the therapeutic effect and potential complications related to these modalities. Of particular value for the individual in training are tables describing the International Federation of Gynecologists and Obstetricians staging for each malignancy. Coupled with this are multiple tables relating stage and/or histologic grade to incidence, nodal spread, chemotherapeutic response, or survival. In addition, Dr Piver goes to great lengths to list almost all treatment modalities available for a given malignancy. Although this may be of great value to the fellow in training, it is likely to be very confusing to students who believe there is one answer to every question. In addition, in striving to be concise, much of the hows and whys of oncology have been omitted, blurring the relationship between disease, and its manifestations.

Part II covers a broad spectrum of clinical problems in gynecology, including benign neoplasms, infertility, infectious diseases, and pelvic relaxation. Each chapter attempts to elucidate the etiologies, symptoms, pertinent physical findings, workup, and diagnosis related to the specific presenting complaint. The selected topics are those most likely to be of interest to the individual in training. In addition, each chapter provides a quick summary of the workup and its diagnostic interpretation, which is invaluable to the office practitioner or the resident in training.

In summary, Dr Piver's *Manual of Gynecologic Oncology and Gynecology* is an excellent quick reference for the individual in training or the office practitioner. Its "just the facts" approach provides clear and concise information for those who already have a basic understanding of gynecologic oncology and gynecology. However, this approach has a price, and

those with less training will find portions of this manual confusing.

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GYNECOLOGY FOR THE HOUSE OFFICER

Edited by Stephen H. Cruilshank, MD, and Allan Chamberlain, MD. 211 pp, illustrated. Baltimore, MD, Williams & Wilkins, 1990. \$17.95 (softcover)

This volume is a convenient and useful reference for both house officers and practitioners. It presents an outline for the diagnosis and management of numerous gynecologic problems. The physical dimensions of the book are such that it can be easily carried in a pocket and taken to a clinic area or the emergency room.

The authors are both knowledgeable and experienced and provide numerous references where readers can expand on the information presented. The writing style makes for easy reading.

The book is divided into several convenient sections which facilitate use. The section on pelvic anatomy contains many valuable operative hints. Although it is well written, it is somewhat too advanced for house officers. Other sections discuss the routine gynecologic examination, pap smears, contraceptive techniques, and sexually transmitted diseases. The section on reproductive endocrinology and infertility is accurate and well written. It presents clinical and diagnostic modalities in a concise fashion as well as therapeutic approaches.

The section on postoperative complications is rather brief as is the one on gastrointestinal complications. This is unfortunate considering the importance of these topics. By comparison, the section on gynecologic oncology is more than adequate for a handbook. It covers all of the needed classifications and therapies and presents information that is important both medically and legally. Finally, the section on special procedures is extremely well done, covering a number of procedures and techniques.

This book achieves its stated purposes. It favorably compares with other texts in the field and is up-to-

date. The small physical size of the book, its conciseness as well as its purchase price, will make it very attractive to house officers. My residents found it to be of great help during their daily rounds and expressed an interest in purchasing it.

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CURRENT PRACTICE OF SURGICAL STAPLING

Edited by Mark M. Ravitch, MD; Felixien M. Steichen, MD; Roger Welter, MD. 324 pp, illustrated. Malvern, PA, Lea & Febiger, 1991. \$79.50 (hardcover)

This text presents the proceedings of an international symposium on surgical stapling held in Luxembourg in 1988. In a clearly written, amply illustrated, authoritative volume, the editors provide a thorough review of current techniques of stapling for pulmonary esophageal, gastric, and colorectal surgery. Worldwide authorship of the 51 chapters highlights the global application of stapling techniques. The volume is a tribute to the late Dr Mark M. Ravitch, one of the editors, who was pivotal in the development of stapling in the United States.

More than a manual of techniques of mechanical suturing, the text provides a valuable historical review, which substantially contributes to an understanding of this modern technology. In addition, separate chapters describe potentially useful techniques involving biological glues and compression devices with plastic rings.

As a compendium of current, state of the art methods of stapling, the book is useful, and the editors' objectives are fulfilled. However, the symposium was underwritten by one manufacturer of stapling devices; others are ignored. In this field it is hard to separate promotion and marketing from objective science, and this text is no exception. In addition, some chapters are unnecessarily repetitive.

Stapling is here to stay. Surely many patients have been spared a colostomy by application of stapling for midrectal cancer. It is, however, hard to find evidence that stapling lessens mortality compared with hand suturing. What little time is saved by stapling techniques may be negated by the additional cost. On the other hand,

stapling methods are probably easier to learn than hand suturing methods. Increasing numbers of surgeons appear to be more adept with stapling than with hand suturing. Trainees need to learn both.

The volume will be of interest to general surgeons and thoracic surgeons and to trainees in these disciplines. The price is reasonable.

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COGNITIVE-BEHAVIORAL MARITAL THERAPY

By Donald H. Caucom, PhD, and Norman Epstein, PhD. 496 pp. New York, Brunner/Mazel Publishers, 1990. \$47.95 (hardcover)

This book presents a cognitive-behavioral, skills-oriented approach to understanding and treating marital discord. The authors, Dr Donald Caucom and Dr Norman Epstein, who are currently in private practice, have both been involved in marital distress research. Dr Caucom has worked for a number of years as Director of Research at the Center for Cognitive Research.

The focus of the book, as stated by the authors, is on the roles that behaviors, cognitions, and emotions play in determining couples' levels of marital satisfaction or distress, and consequently the roles that they play in the treatment of marital problems. They attempt to do this by introducing theory, research, and clinical practice for a treatment approach that incorporates structure into the clinical setting, and they clarify the numerous decisions regarding intervention that must be made in each session.

The book is organized according to three constructs: behavior, cognition, and affect. Although the authors acknowledge that these domains are integrally related, each of the constructs is considered separately with numerous comments and examples on ways in which they are or may be integrated.

The first section of the book describes both the theoretical issues and empirical research findings that have identified a variety of specific behavioral, cognitive, and affective factors that help to differentiate distressed from nondistressed couples. The second section contains detailed descrip-

tions of interviews, questionnaires, and behavioral observation methods, and the final section offers numerous intervention strategies for addressing the various components of marital distress.

The authors admit this book is not for the novice, since it omits issues rather basic to the field of marital therapy, such as establishing rapport, the use of co-therapists and responding to confidential information from one spouse. In addition, several specialty areas such as the behavioral treatment of sexual dysfunctions and spouse abuse have not been included.

This book offers a refreshing, active approach to marital discord, giving many examples and research findings to help emphasize critical areas, by providing structure without ignoring the complexities involved in treating couples in distress.

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ETHICS IN MEDICINE: INDIVIDUAL INTEGRITY VERSUS DEMANDS OF SOCIETY

(Karolinska Institute Nobel Conference Series). Edited by Peter Allebeck, MD, and Bengt Jansson, MD. 240 pp. New York, Raven Press, 1990. \$99.00 (hardcover)

This volume is a transcript of presentations given at the third meeting of the first world congress in medical ethics under the auspices of the Karolinska Institute Nobel Conference Series. The very occurrence of an international conference on medical ethics is remarkable, and without passing judgment on the intrinsic merit of the contents, makes this publication interesting.

Unfortunately, the intrinsic merit of the contents is mixed. A range of topics, pulled together under the broad title of *Individual Integrity Versus Demands of Society*, constitute the book. The mosaic of topics are reflected by the mosaic of speakers, some of whom have world standing and others of whom are without obvious authority.

Two chapters (presentations) in particular have the potential for making a lasting contribution to medical ethics. The first is the piece by Edmund D. Pellegrino on "The rela-

tionship of autonomy and integrity in medical ethics." Here Pellegrino attacks the dominance that the notion of autonomy enjoys in current Western (especially American) thought. He seeks to replace it with the more comprehensive notion of integrity. Indeed, the notion as Pellegrino uses it makes use of several themes, each corresponding approximately to the different meanings of the word integrity: corporeal, psychological, and axiological (to use the authors terms). Although much expansion of the notions put forth would be needed Pellegrino is certainly onto something fundamental needed to counterbalance the almost tyrannical dominance that the notion of autonomy has wielded in recent times.

The other promising piece in the book is by E. Keyserlingk from The McGill Center for Medicine, Ethics, and Law. He asks the question, appropriate for this international conference, of whether a code of ethics can be universally applicable in a multicultural world. This almost fantastic possibility is approached with realism, thoughtfulness, and modesty. The reader is indeed inclined to find the goal of a universal code of ethics appealing and plausible.

Another section of the book concerns the setting of priorities in the health care system and focuses on a presentation by D. Callahan. This piece is a brief summary of the views laid out in his book *Setting Limits*. Neither the presentation nor the discussion are superior to the book itself and the commentary that it generated in its own right.

The final section of the book concerns the ethical aspects of human immunodeficiency virus infection. Again, the presentations are interesting, but they do not add much in content or quality to the existing peer review publications.

The book has a place on the library shelves of ethics institutes, earned by its potential for stimulating further thought. It is certainly not earned by its technical features, which include endless typographic errors. It is not a required purchase for lay people, students or other professionals who are interested in learning some medical ethics.

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BOOKS RECEIVED

CARDIOLOGY

Progress in Cardiology. Edited by Douglas P. Zipes, MD, and Derek J. Rowlands, MD. 138 pp. Malvern, Pa, Lea & Febiger, 1991. \$39.50 (softcover)

GERIATRICS

Facilitating Self Care Practices in the Elderly. Edited by Barbara J. Horn, RN, PhD. 185 pp. Binghamton, NY, The Haworth Press, Inc, 1990. \$24.95 (hardcover)

HISTORY OF MEDICINE

Medical Odysseys. The Different and Sometimes Unexpected Pathways to Twentieth Century Medical Discoveries. By Allen B. Weisse, MD. 250 pp. New Brunswick, NJ, Rutgers University Press, 1991. \$36.00 (hardcover), \$13.95 (softcover)

A History of Contraception: From Antiquity to the Present Day. By Angus McLaren. 275 pp. Cambridge, Mass, Basil Blackwell, Inc, 1991. \$36.95 (hardcover)

The Ambulance. The Story of Emergency Transportation of Sick and Wounded Through the Centuries. By Katherine Traver Barkley. 207 pp, illustrated. Kiamesha Lake, NY, Load-N-Go Press, 1990. \$13.95 (softcover)

History of Syphilis. By Claude Quétel. Translated by Judith Braddock and Brian Pike. 342 pp, illustrated. Baltimore, Md, The Johns Hopkins University Press, 1990. \$39.95 (hardcover)

INFECTIOUS DISEASES

Recognition, Identification, and Prevention of Acute Viral Infections. By Donald M. McLean, MD. 375 pp, illustrated. St Louis, Mo, Warren H. Green, Inc, 1991. \$42.50

INTERNAL MEDICINE

The Foot in Diabetes. By G. James Sammarco, MD. 235 pp, illustrated. Malvern, Pa, Lea & Febiger, 1991. \$45.00

Rheumatology for the Health Care Professional. Edited by Harry Spiera, MD, and Irwin Oreskes, PhD. 369 pp, illustrated. St Louis, Mo, Warren H. Green, Inc, 1991. \$42.50.

Practical Guide to the Care of the Medical Patient. By Fred F. Ferri, MD. Second Edition. 804 pp, illustrated. St Louis, Mo, Mosby-Year Book, Inc, 1991. \$25.95 (softcover)

MISCELLANEOUS

Love Letters Between a Certain Late Nobleman and the Famous Mr. Wilson. Edited by Michael S. Kimmel, PhD. 124 pp. Binghamton, NY, The

Haworth Press, Inc, 1990. \$22.95 (hardcover) \$11.95 (softcover)

The Doctrine of Signatures: A Defense of Theory in Medicine. Second Edition. By Scott Buchanan. Edited by Peter P. Mayock, Jr, MD, and with a foreword by Edmund D. Pellegrino, MD. 205 pp. Champaign, Ill, University of Illinois Press, 1991. \$34.95 (hardcover) \$10.95 (softcover)

Bad Boys and Tough Tattoos. A Social History of the Tattoo with Gangs, Sailors, and Street-Corner Punks. By Samuel M. Steward, PhD. 198 pp. Binghamton, NY, The Haworth Press, Inc, 1990. \$19.95 (hardcover)

Finding Love in a Cold World. By Sheldon Cholst, MD. 189 pp. New York, Beau Rivage Press, 1990. \$14.95 (softcover)

Jewish Values in Health and Medicine. Edited by Rabbi Levi Meier, PhD. 201 pp. Latham, Md, University Press of America, 1991. \$16.75 (softcover)

NEUROLOGY

Essentials of Child Neurology. By Suresh Kotagal, MD. 196 pp, illustrated. St Louis, Mo, Ishiyaku EuroAmerica, Inc, 1990. \$42.50 (hardcover)

ONCOLOGY

The Toxicity of Anticancer Drugs. Edited by Garth Powis, D. Phil, and Miles P. Hackers, PhD. 228 pp. Elmsford, NY, Pergamon Press, Inc, 1991. \$49.50 (hardcover)

OPHTHALMOLOGY

Eye Trauma. Edited by Bradford J. Shingleton, MD, Peter S. Hersh, MD, and Kenneth R. Kenyon, MD. 427 pp, illustrated. St Louis, Mo, Mosby-Year Book, Inc, 1991. \$99.00 (hardcover)

Surgery of the Ear. Fourth Edition. By Michael E. Glasscock, III, and George E. Shambaugh, Jr. 640 pp, illustrated. Philadelphia, Pa, WB Saunders, 1990. \$125.00 (hardcover)

PATHOLOGY

Current Surgical Pathology. By Michael J. Warhol, MD. 144 pp, illustrated. Philadelphia, Pa, BC Decker, Inc, 1990. \$49.50 (hardcover)

PSYCHIATRY

Psychiatry Specialty Board Review. By William M. Easson, MD, and Nicholas L. Rock, MD. 160 pp. New York, Brunner/Mazel Publishers, 1991. \$19.95 (softcover)

Diversity and Complexity in Feminist Therapy. Edited by Laura S. Brown, PhD, ABPP, and Maria P.P. Root, PhD. 336 pp. Binghamton, NY, The Haworth Press, Inc, 1990. \$34.95 (hardcover)

We Heard the Angels of Madness. One Family's Struggle with Manic Depression. By Diane Berger and Lisa Berger. 212 pp. New York, William Morrow & Co, 1991. \$19.95 (hardcover)

Psychotherapy with Lesbian Clients: Theory Into Practice. By Kristine L. Falco, PhD. 224 pp. New York, Brunner/Mazel Publishers, 1991. \$26.95 (hardcover)

Synopsis of Psychiatry. Behavioral Sciences. Clinical Psychiatry. Sixth Edition. By Harold I. Kaplan, MD, and Benjamin J. Saddock, MD. 903 pp. New York, Williams & Wilkins, 1991. \$44.00 (hardcover)

Sexual Dilemmas for the Helping Professional. by Jerry Edewich, MSW, and Archie Brodsky. 272 pp, New York, Brunner/Mazel Publishers, 1991. \$19.50 (softcover) \$32.50 (hardcover)

Comparing Psychoanalytic Psychotherapies. Developmental, Self, and Object Relations; Self Psychology; Short-Term Dynamic. By James F. Masterso, MD, Marian Tolpin, MD, and Peter E. Sifneos, MD. 298 pp. New York, Brunner/Mazel Publishers, 1991. \$37.50 (hardcover)

Clinical Hypnosis With Children. Edited by William C. Wester II, EdD, and Donald J. O'Grady, PhD. 272 pp. New York, Brunner/Mazel Publishers, 1991. \$32.95 (hardcover)

Compulsive Exercise and the Eating Disorders. Toward an Integrated Theory of Activity. By Alayne Yates, MD. 259 pp. New York, Brunner/Mazel Publishers, 1991. \$31.95 (hardcover)

PHYSIOLOGY

The Heart. Physiology and Metabolism. Second Edition. By Lionel H. Opie, MD. 513 pp, illustrated. New York, Raven Press, 1991. \$68.00 (hardcover)

RADIOLOGY

Magnetic Resonance Imaging of Children. By Mervyn D. Cohen, MB, ChB, and Mary K. Edwards, MD. 983 pp, illustrated. Philadelphia, BC Decker Inc, 1990. \$169.50. (hardcover)

MR and CT Imaging of the Head, Neck, and Spine. Volume I and II. 1,371 pp, illustrated (Vol I); 663 pp, illustrated (Vol II). Edited by Richard E. Latchaw, MD. St Louis, Mo, Mosby-Year Book, Inc, 1991. \$225.00 (2 volume set). (hardcover)

Atlas of Roentgenographic Measurement. By Theodore E. Keats, MD. 710 pp, illustrated. St Louis, Mo, Mosby-Year Book, Inc, 1990. \$95.00. (hardcover)

SUBSTANCE ABUSE

Addiction Potential of Abused Drugs and Drug Classes. Edited by Carlton K. Erickson, PhD; Martin A. Javors, PhD; William W. Morgan, PhD,

(Guest Editors) Barry Stimmel, MD, (Editor) 201 pp. Binghamton, NY, The Haworth Press, Inc, 1990. \$29.95 (hardcover)

Russian Drinking: Use and Abuse of Alcohol in Pre-Revolutionary Russia. By Boris M. Segal, MD. 383 pp. New Brunswick, NJ, Rutgers Center of Alcohol Studies, 1987. \$19.95 (softcover)

The Drunken Society: Alcohol Abuse and Alcoholism in the Soviet Union. By Boris M. Segal, MD. 618 pp. New York, Hippocrene Books, 1990. \$40.00 (hardcover)

Crack Cocaine: A Practical Treatment Approach for the Chemically Dependent. By Barbara C.

Wallace, PhD. 320 pp. New York, Brunner/Mazel Publishers, 1991. \$36.95 (hardcover)

SURGERY

The Breast. Comprehensive Management of Benign and Malignant Diseases. Edited by Kirby I. Bland, MD, and Edward M. Copeland, III, MD. 1,154 pp, illustrated. Philadelphia, Pa, WB Saunders Company, 1991. \$150.00 (hardcover)

The Fracture Classification Manual. By Ramon B. Gustilo, MD, Melissa A. Hanson, Tracy D. Davis. 175 pp, illustrated. St Louis, Mo, Mosby-Year Book, Inc, 1991. \$45.00 (softcover)

AUDIO TAPES

Getting Your Baby To Sleep (And Back to Sleep). By Vicki Lansky. 60 minutes. Fairview, NC, High Windy Audio. 1990. \$9.98.

Imagine Yourself to Sleep. Vol 2: Guided Imagery and Nature Sounds for Kids. 60 minutes, Asheville, NC, Audio Outings, 1990. \$9.98

VIDEO TAPE

Sexual Dysfunction: Myths, Facts, and Solutions. 41 minutes. Produced by Editel, Boston, Mass. 1991, \$24.95

FROM THE LIBRARY

COCAINE

"Crack" cocaine is a form of unrefined or unpurified freebase. Crack is made by combining cocaine hydrochloride with an agent such as baking soda and cooking it in water, creating an oil-like substance. The oil separates from the water and solidifies into small chunks, which can be from 25% to 90% pure. The resulting substance resembles rock salt and can be smoked in pipes and cigarettes. Smoked "crack" cocaine moves rapidly into the bloodstream and reaches target organs (eg, the brain) in one circulation time. This creates an instantaneously high blood saturation; hence, intense euphoria. (If 15 mg of cocaine HCl "snorted" provided a recognized "high," imagine the "rush" of 50 to 100 mg smoked as the base!) Smoking has renewed popularity for another reason: It avoids needle use and thus some of the fear of AIDS transmission.

GEORGE R. GAY, MD
(*NY State J Med* 65:384-386)

Physical activity reduces risk of noninsulin-dependent diabetes mellitus

Prominent risk factors for noninsulin-dependent diabetes mellitus (NIDDM) include family history of diabetes, obesity, advancing age, and history of hypertension. A recent report demonstrated that physical activity "had a protective effect against the development of NIDDM in middle-aged men;" this effect was independent of other risk factors (*N Engl J Med* 1991; 325:147-152). Of further importance is that this protective effect is even greater for persons at high risk for NIDDM.

As leisure-time physical activity increased in increments of 500 kcal/week, the occurrence of NIDDM dropped by 6%. Vigorous exercise had a stronger protective effect than did moderate exercise, although all levels of physical activity led to reduced relative risk.

The study population consisted of 5,990 men who had completed questionnaires on lifestyle and health in 1962 and again in 1976. The authors assessed the relationship between various risk factors for NIDDM and the incidence of diabetes during the 14-year interval between the surveys.

Lyme disease: Two reports focus on cardiac disorders and arthritis

Lyme disease, or infection with the tick-borne spirochete *Borrelia burgdorferi*, is a serious health problem in many regions nationwide. The multisystemic effects of the disease often mimic other disorders and, if not properly treated, can linger and progress for many years after the initial infection.

In one recent study, the investigators demonstrated that Lyme borreliosis may have been the cause of atrioventricular block in men who had received permanent pacemakers. Heart block is a common cardiac effect of Lyme borreliosis; it is a temporary condition, and affected patients would not usually require a permanent pacemaker. In this controlled study, the investigators evaluated 35 men with pacemakers and a history of heart block of unknown cause; each underwent blood tests for *B burgdorferi*. "The mean OD of antibodies to *B burgdorferi* of the patients was significantly ($p = 0.05$) higher than that of the controls . . ."

The authors found that four of the patients with pacemakers were seropositive for *B burgdorferi* and that the heart block had lessened or no longer existed in three of these four patients. Of the 31 seronegative patients, only one had reduced heart block. The heart block in the three seropositive patients may have been caused by Lyme borreliosis and would have decreased or disappeared without the need for a pacemaker.

In a separate study, undertaken in 1988-1989, Szer et al reported on 46 children who had been diagnosed with Lyme arthritis in 1976-1979 (*N Engl J Med* 1991; 325:159-163). In the 1970s, antibiotics were generally not used in the treatment of Lyme disease.

Erythema migrans was the presenting symptom in the majority of cases; accompanying symptoms included headache and stiff neck, fever, lethargy, myalgia, and anorexia. Intermittent joint pain was present in 45 of 46 children during the first weeks of the disease. From two weeks to two years (median of 3.4 months) after the initial illness, brief episodes of frank arthritis were noted in all of the children. The knee was affected in 98% of cases, and sometimes the elbow, ankle, hip, and wrist were also affected.

"There was a direct correlation between the age at the onset of infection and the total duration of arthritis ($r = 0.3, p < 0.05$)." In general, the episodes of arthritis became less frequent after the first year; however, during the second and third years, the length of each attack often increased, with episodes lasting weeks or months. Five of 46 children still had bouts of arthritis six years after the original illness.

In 1988-1989, 39 of 46 children were contacted, and 12 of 39 (31%) occasionally still experienced joint pain. The authors suggested that in some instances, "residual spirochetal infection of synovial tissue" may have caused these joint symptoms. Evaluation of blood samples 12-13 years after the diagnosis of Lyme arthritis revealed that IgG titers were higher and IgM responded more prevalent among the patients with long-term joint symptoms.

FDA is evaluating silicone breast implants

When the US Food and Drug Administration (FDA) was given the responsibility of approving medical devices in 1976, silicone breast implants were already on the market. After passage of the 1976 law, manufacturers of existing medical devices were required to amass data on the effectiveness of the devices and the frequency and characteristics of adverse effects, while the devices continued in use. Because of recent questions about the safety of silicone-gel-filled breast implants, the FDA is evaluating these data, and by the end of 1991 will determine whether the silicone breast implants can remain on the market (*FDA Medical Bulletin* 1991; 21:3). Potential problems with the various implants include carcinogenicity as the implants degrade, effects of the fibrous tissue that grows around the implant, and difficulty in mammographic detection of breast abnormalities.

Blood cholesterol screening project reports good response rate

The National Institutes of Health has recommended that all adults be tested for their blood cholesterol level. The Massachusetts Department of Public Health (MDPH) was part of a research project to evaluate the effectiveness of a mass screening program for blood cholesterol (*JAMA* 1991; 266:375-381). In 1986, the MDPH began offering free screenings at various loca-

tions in four communities. The communities represented a variety of racial, ethnic, and socioeconomic populations. The program required a fingerstick blood sample for testing on a portable cholesterol analyzer, a five-minute counseling session with a health educator, and follow-up telephone calls or postcards reminding persons with high blood cholesterol to consult a physician.

Of the 10,428 individuals screened, 25.2% (2,627) were found to have high blood cholesterol levels and were included in the follow-up efforts. At the 2-4 month

follow-up, 51.5% of those who completed the follow-up questionnaire had seen a physician.

The authors found that in spite of their efforts, "The young, males, blacks, Hispanics, the poor, those with less education, and those without health insurance were underrepresented in the screenings." In addition, the authors were concerned that, "there appears to be overreliance on pharmacologic agents by physicians for managing this condition, particularly among the elderly." Dietary modification should be the treatment of choice for high blood cholesterol.

FROM THE LIBRARY

DIETARY FATS AND BLOOD CHOLESTEROL LEVELS IN ELDERLY PERSONS A Ten Year Study

A ten-year study of the efficacy of dietary control of blood cholesterol in 137 elderly women with long-established food habits was undertaken. Corn oil margarine and peanut oil were substituted over a five-year period for conventional animal and hydrogenated vegetable shortenings in preparation and serving of all meals. Blood cholesterol levels decreased significantly in most of the women during the first eighteen to twenty-four months but subsequently began to rise, and within thirty-six to forty-eight months, most of the remaining subjects had returned to their base line levels. Substitution of a corn oil margarine in preparation of food for 34 male and female patients with arteriosclerotic heart disease in another institution was associated with biochemically significant decreases in blood cholesterol in 5 of 17 patients who had had myocardial infarction and in 10 of 17 patients without myocardial infarction.

ANTHONY A. ALBANESE, PhD

MAURICE L. WOODHULL, MD

EDWARD J. LORENZE, MD

LOUISE A. ORTO, MS

(*NY State J Med* 65:517-529)

OBITUARY LISTINGS

Walter Harold Camp, MD, Bellingham, Washington. Died May 24, 1991; age 78. Dr Camp was a 1938 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Diplomate of the American Board of Radiology. He was a member of the Radiological Society of North America, Inc, the Medical Society of the County of Fulton, and the Medical Society of the State of New York.

Walter Constantine, MD, Tequesta, Florida. Died June 22, 1991; age 90. Dr Constantine was a 1926 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. His memberships included the New York Academy of Medicine, the New York Ophthalmology Society, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

George L. Ginsberg, MD, New York. Died February 16, 1991; age 56. Dr Ginsberg was a 1959 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Psychiatry and Neurology and a Fellow of the American Psychiatric Association. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Bernhardt S. Gottlieb, MD, Larchmont. Died June 16, 1991; age 93. Dr Gottlieb was a 1921 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychiatric Association, the Association for Research in Nervous and Mental Disease, the Pan American Medical Association, the American Psychoanalytic Association, the New York County Medical Society, and the Medical Society of the State of New York.

Martin Arthur Green, MD, Great Neck. Died June 21, 1991; age 71. Dr Green was a 1945 graduate of the University of Michigan Medical School, Ann Arbor. He was a Diplomate of the American Board of Psychiatry and Neurology and a Fellow of the Ameri-

can College of Physicians. His memberships included the American Academy of Neurology, the American Psychiatric Association, the Association for Research in Nervous and Mental Disease, the Nassau County Medical Society, and the Medical Society of the State of New York.

Robert A. Herfort, MD, Castine, Maine. Died May 1, 1991; age 72. Dr Herfort was a 1942 graduate of the New York University School of Medicine. He was a Diplomate of the American Board of Surgery and a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Louis John Iacovino, MD, Homer. Died March 22, 1991; age 90. Dr Iacovino was a 1926 graduate of Tufts University School of Medicine, Boston, Massachusetts. He was a member of the Cortland County Medical Society and the Medical Society of the State of New York.

Joseph H. Krug, MD, Englewood, New Jersey. Died May 4, 1991; age 75. Dr Krug was a 1940 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Ophthalmology and a Fellow of the American College of Surgeons. His memberships included the New York Academy of Medicine, the American Academy of Ophthalmology and Otolaryngology, the New York County Medical Society, and the Medical Society of the State of New York.

Michael L. Lewin, MD, Cliffside Park, New Jersey. Died May 15, 1991; age 82. Dr Lewin was a 1933 graduate of the Medizinische Fakultät, Universität Zurich, Zurich, Switzerland. He was a Diplomate of the American Board of Plastic Surgery, a Diplomate of the American Board of Otolaryngology, a Qualified Fellow of the International College of Surgeons, and a Fellow of the American College of Surgeons. His memberships included the New York Academy of Medicine, the New York Society for Surgery of the Hand, the American Association of Plastic Surgeons, the American Society of Maxillofacial Surgeons, the

American Society of Plastic & Reconstructive Surgery, the American Academy of Otolaryngology, the Bronx County Medical Society, and the Medical Society of the State of New York.

Fathallah C. Maghak, MD, Yonkers. Died December 11, 1990; age 67. Dr Maghak was a 1952 graduate of Alexandria University, Faculty of Medicine, Alexandria, Egypt. She was a Fellow of the American College of Obstetricians and Gynecologist. She was a member of the New York Academy of Medicine, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Harold Marcus, MD, New York. Died March 9, 1991; age 69. Dr Marcus was a 1950 graduate of the University of Chicago, Pritzker School of Medicine. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychiatric Association, the American Psychoanalytic Association, the New York County Medical Society, and the Medical Society of the State of New York.

Elliot Oppenheim, MD, New York. Died May 17, 1991; age 76. Dr Oppenheim was a 1938 graduate of the University of Edinburgh, Faculty of Medicine, Edinburgh, Scotland. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. His memberships included the New York Gastroenterological Society, the Clinical Society, New York Diabetes Association, the New York State Society of Internal Medicine, the American Society of Internal Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

Thomas J. Parks, MD, Oyster Bay. Died June 11, 1991; age 88. Dr Parks was a 1927 graduate of Tulane University School of Medicine, New Orleans, Louisiana. He was a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Surgeons, and a Fellow of the American College of Obstetricians and Gynecologist. His memberships included the New York Academy of

Medicine, the New York Obstetrical Society, the American Fertility Society, the American Geriatrics Society, the New York County Medical Society, and the Medical Society of the State of New York.

Patrick A. Pilosi, MD, Kew Gardens. Died September 20, 1990; age 82. Dr Pilosi was a 1937 graduate of St Louis University School of Medicine, St Louis, Missouri. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Alexius Rachun, MD, Ithaca. Died October 19, 1990; age 80. Dr Rachun was a 1940 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a member of the Medical Society of the County of Tompkins and the Medical Society of the State of New York.

Alice Ellen Rost, MD, Albany. Died May 24, 1991; age 93. Dr Rost was a 1922 graduate of Schlesische-Friedrich-Wilhelms Universitaet Medizinische Fakultet, Breslau, Germany. She was a Diplomate of the American Board of Psychiatry and Neurology and a Fellow of the American Psychiatric Association. She was a member of the American Academy of Neurology, the Medical Society of the County of Albany, and the Medical Society of the State of New York.

Leonor Lomotan Samano, MD, Corona. Died April 14, 1991; age 56. Dr Samano was a 1962 graduate of the Ramon Magsaysay Memorial Medical Center, University of the East, Quezon City, Philippines. She was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

William Schwartz, MD, Hicksville. Died May 30, 1991; age 68. Dr Schwartz was

a 1951 graduate of the University of Health Science Chicago Medical School. He was a Diplomate of the American Board of Pediatrics and a Fellow of the American Academy of Pediatrics. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Manfred Sinnreich, MD, Scarsdale. Died June 5, 1991; age 65. Dr Sinnreich was a 1952 graduate of Medicinski Fakultet, Sveucilista u Zagrebu, Zagreb, Yugoslavia. He was a member of the American Society of Bariatric Physicians, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Louis Samuel Smith, MD, Boynton Beach, Florida. Died April 1, 1991; age 71. Dr Smith was a 1942 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Obstetricians and Gynecologists, and a Qualified Fellow of the International College of Surgeons. He was a member of the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Louis Harold Spector, MD, Pultneyville. Died May 17, 1991; age 80. Dr Spector was a 1937 graduate of Rush Medical College of Rush University. He was a Fellow of the American Academy of Family Physicians. His memberships included the New York Academy of Medicine, the New York Pathological Society, the Medical Society of the County of Monroe, and the Medical Society of the State of New York.

Norman Steinhauff, MD, Middle Island. Died June 2, 1991; age 50. Dr Steinhauff was a 1970 graduate of Medizinische Fakultet der Ludwig

Maximilians Universitaet, Munchen, Bayern, Germany. He was a Diplomate of the American Board of Family Practice and a Fellow of the American College of Emergency Physicians. He was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Edmund V. Taglianetti, MD, Staten Island. Died June 18, 1991; age 73. Dr Taglianetti was a 1944 graduate of the Medical College of Wisconsin, Milwaukee, Wisconsin. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Vincent Joseph Tesoriero, MD, Durham, North Carolina. Died May 2, 1991; age 85. Dr Tesoriero was a 1932 graduate of Columbia University College of Physicians and Surgeons. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Paul Weiss, MD, Yonkers. Died February 15, 1991; age 82. Dr Weiss was a 1936 graduate of the Universitaet Wien, Medizinische Fakultet, Wien, Austria. He was a member of the American Geriatrics Society, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Staffan N. Westin, MD, Locust Valley. Died June 14, 1991; age 49. Dr Westin was a 1968 graduate of Karolinska Medico, Kirurgiska Institutet, Stockholm, Sweden. He was a Diplomate of the American Board of Anesthesiology and a Fellow of the American College of Anesthesiologists. He was a member of the American Society of Anesthesiologists, Inc, the Nassau County Medical Society, and the Medical Society of the State of New York.

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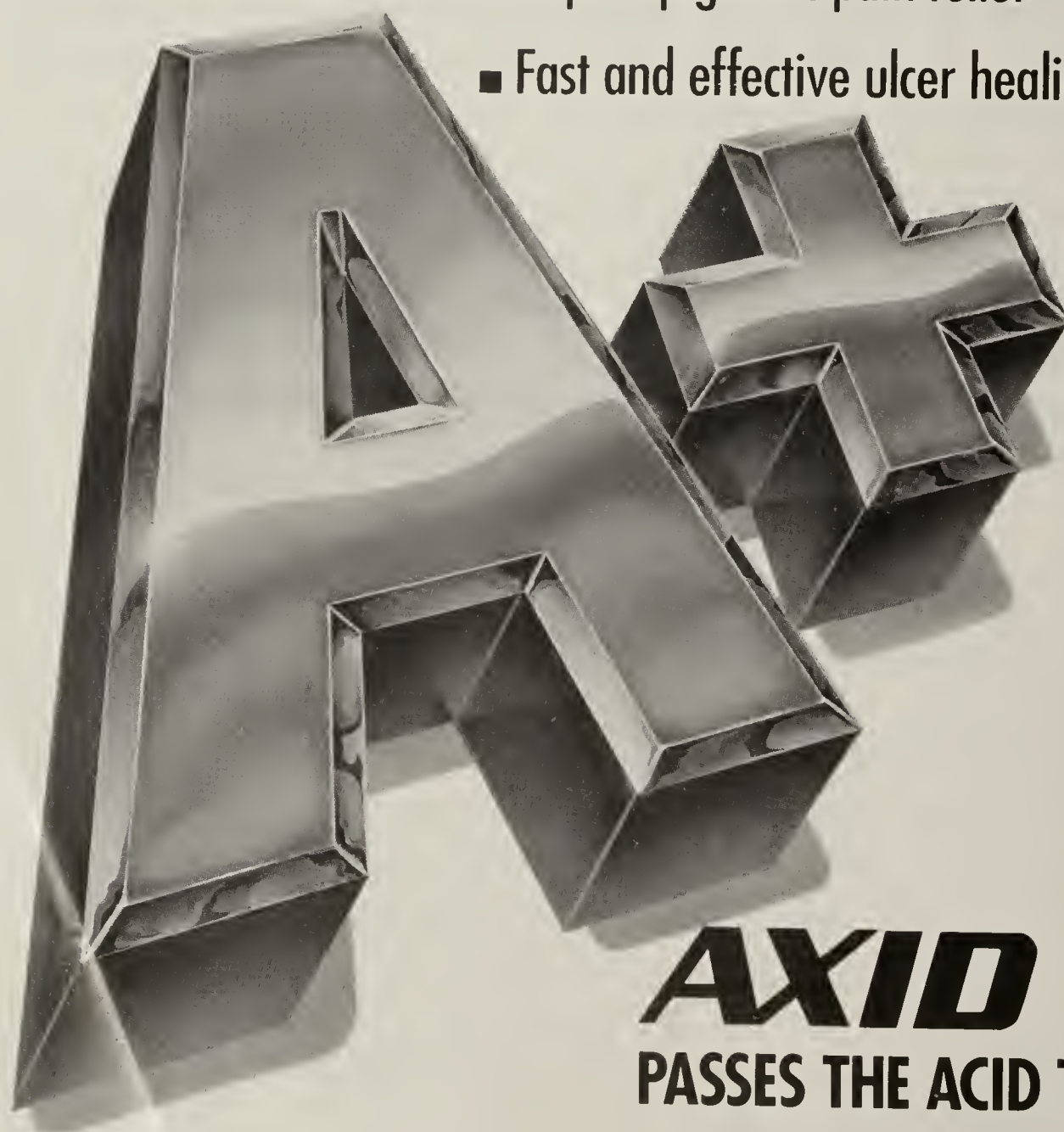
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Brief Summary. Consult the package insert for complete prescribing information.
Indications and Usage: 1. Active duodenal ulcer—for up to 8 weeks of treatment. Most patients heal within 4 weeks.

2. Maintenance therapy—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H₂-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

Precautions: General—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests: False-positive tests for urobilinogen with Multistix[®] may occur during therapy.

Drug Interactions: No interactions have been observed with theophylline, chlorazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C: Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live litters, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic: Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular: In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS: Rare cases of reversible mental confusion have been reported.

Endocrine: Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic: Fetal thrombocytopenia was reported in a patient treated with nizatidine and another H₂-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental: Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity: As with other H₂-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other: Hyperviscemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

PV 2091 AMP
(0911190)

References

1. Data on file, Lilly Research Laboratories.
2. *Scand J Gastroenterol* 1987;22(suppl 136):61-70.
3. *Scand J Gastroenterol* 1987;22(suppl 136):47-55.
4. *Am J Gastroenterol* 1989;84:769-774.

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Additional information available to the profession on request



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(continued from p 9A)

graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 263-5295.

Oct 3. Overcoming Chronic Airways Disease. 7 Cat I Credits. Waldorf Astoria. *Oct 10-11. 14th Annual Current Concerns in Adolescent Medicine.* 12 Cat I Credits. New York Hilton. *Oct 19-20. Complications in Urology.* Long Island Jewish Medical Center. Contact: Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042. Tel: (718) 470-8650.

Oct 16-19. Renal Biopsy in Medical Diseases of the Kidney. 23 Cat I Credit. Columbia University. Contact: Center for Continuing Education, College of Physicians & Surgeons of Columbia University, 630 W 168th St, New York, NY 10032. Tel: (212) 305-3682.

UNIONDALE

Oct 4-5. Neck and Back Pain: Diagnosis and Management. Long Island Marriott. Contact: Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042. Tel: (718) 470-8650.

WHITE PLAINS

Oct 11 and 12. Prostate Cancer in the 90s: Advances in Diagnosis and Treatment. Holiday Inn-Crowne Plaza Hotel. Contact: Dina A. Mastoras, Administrator, Department of Radiation Medicine, New York Medical College, Valhalla, NY 10595. Tel: (914) 285-8560.

AROUND THE NATION

ARIZONA

Oct 17-21. The Spine: Current Concepts of Diagnosis and Treatment. Scottsdale Princess, Scottsdale. Contact: The Spine Study Group, c/o UnConventional, Inc, 3960 Park Blvd, Suite E, San Diego, CA 92103. Tel: (619) 692-9115.

CALIFORNIA

Oct 2-6. Current Concepts of Mag-

netic Resonance Imaging/Physics. 19 Cat I Credits. Silverado Hotel, Napa Valley. *Oct 17-20. 1991 Annual Scientific Meeting of the Western Neuroradiological Society.* Ritz-Carlton Resort Hotel, Laguna Niguel. *Oct 26-27. MR Imaging of the Musculoskeletal System: State of the Art.* 9 Cat I Credits. Hotel Del Coronado, San Diego. *Oct 28-Nov 1. 16th Annual San Diego Postgraduate Radiology Course.* 28½ Cat I Credits. Hotel Del Coronado, San Diego. Contact: Dawne Ryals, Ryals and Associates, PO Box 1925, Roswell, Georgia 30077-1925. Tel: (404) 641-9773.

Oct 20. Magnetic Resonance Angiography. Hyatt Regency Hotel, San Francisco. *Oct 21-25. Clinical Magnetic Resonance Imaging.* Hyatt Regency Hotel, San Francisco. *Oct 26-27. Vascular Ultrasound: State of the Art.* Ritz-Carlton Hotel, San Francisco. Contact: Radiology Postgraduate Education, University of California San Francisco School of Medicine, Box 0628, Room C-324, San Francisco, CA 94143. Tel: (415) 476-5731.

Oct 23-26. Trends in OB-GYN Management. 16 Cat I Credits. Hotel Del Coronado, San Diego. Contact: Continuing Medical Education, Sharp Memorial Hospital, 7901 Forst St, San Diego, CA 92123. Tel: (619) 541-4530.

FLORIDA

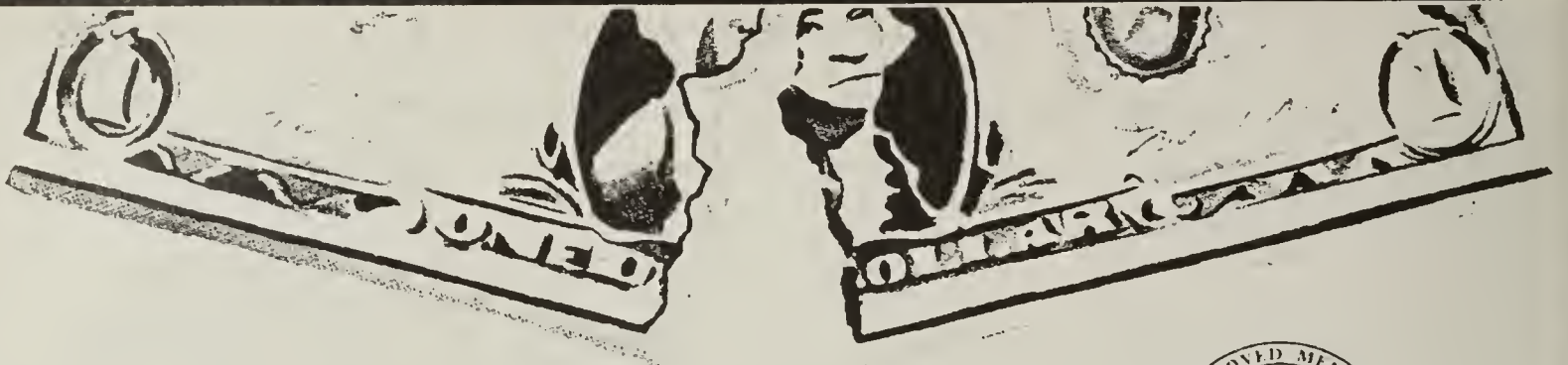
Oct 28, Nov 1. 17th Annual Education Conference of the American Association of Pathologists' Assistants (AAPA). Contact: Doris Schuler-Maloney, Mercy Hospital Medical Center, Department of Pathology, 6th and University, Des Moines, Iowa 50314. Tel: (515) 247-4478.

GEORGIA

Oct 17-20. 38th Annual Meeting Academy of Psychosomatic Research, Consultation-Liaison Research. Marriott Marquis, Atlanta. Contact: Executive Director, Academy of Psychosomatic Medicine, 5824 N Magnolia, Chicago, Ill 60660. Tel: (312) 784-2025.

LOUISIANA

Oct 8-13. 42nd Annual Workshops and Scientific Program of the Society for Clinical and Experimental Hypno-
(continued on p 16A)



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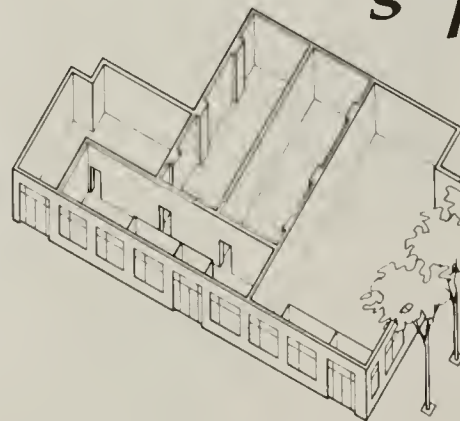
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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

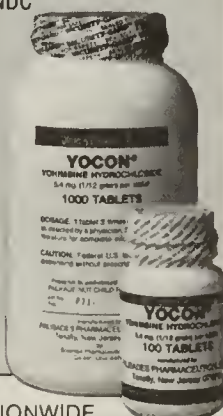
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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(continued from p 13A)

sis. 43 Cat I Credits. Clarion Hotel, New Orleans. Contact: Marion Kenn, Administrative Director, SCEH, 128A Kings Park Dr, Liverpool, New York 13090.

MARYLAND

Oct 25-27. Third Annual Infectious Disease Review Course. Crowne Plaza Hotel, Rockville. Contact: Center for Bio-Medical Communication, Inc, 80 W Madison Ave, Dumont, New Jersey 07628. Tel: (201) 385-8080.

PENNSYLVANIA

Oct 25-27. It's About Time: Recharging the Professional's Battery. Sterling Inn, South Sterling. **Nov 8-10.** Shawnee Inn, Shawnee. Contact: Keith Sedlack, MD, 239 E. 79th St, New York, NY 10021. Tel: (212) 288-9303. □



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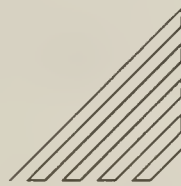
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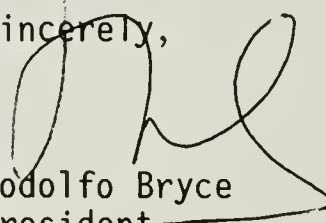
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COOPERSTOWN

Nov 6. Diabetes and Its Complications. 3 Cat I Credits. Bassett Hall Conference Center. Contact: Charlotte L. Hoag, Medical Education Coordinator, Office of Medical Education, The Mary Imogene Bassett Hospital, One Atwell Rd, Cooperstown, NY 13326. Tel: (607) 547-3820.

MANHATTAN

Nov 9. Fiberoptic Endoscopy Workshop for the Management of the Difficult Airway. NYU Medical Center Alumni Hall. **Nov 16. Selegiline: New Applications in Neurological and Psychiatric Disorders.** NYU Medical Center. Contact: NYU Medical Center, Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 263-5295.

Nov 14-16. Rhinoplasty: State of the Art. Waldorf Astoria. Contact: Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear, and Throat Hospital, 210 E 64th St, New York, NY 10021. Tel: (212) 838-9200 Ext 2776.

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Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdose. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Ampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and decrease the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

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INDICATIONS AND USAGE: Zantac® is indicated in:

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3. The treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome and systemic mastocytosis).

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Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy.

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PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy. 2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

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Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Headache, sometimes severe, seems to be related to Zantac® administration. Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and, rarely, pancreatitis have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, atrioventricular block, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocellular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Although controlled studies have shown no antiandrogenic activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonsful equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

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COMMENTARIES

Challenges facing the medical profession

I shall not yield to the temptation to recite the litany of problems that oppress our profession. You have heard it all, all too many times, and the weight of it, I fear, is depressing and immobilizing us. Rather, I would share with you my personal belief that we do ourselves and our profession a severe disservice if we submit to the logic that we, alone, have been singled out by a pernicious and ungrateful society for special abuse.

In this new age of information, there are no safe havens for sacred cows. No group is immune from public scrutiny or question. Medicine is not being singled out as the only group by an inquiring public. In an Age of Information, computers, television, radio, and print media flood the public with data on every aspect of human endeavor. An informed public will not tolerate an attitude of "just trust me, I know what's best for you." You and I will not accept that from those with whom we deal, is there any reason for us to believe our patients will be any more trusting of us?

If questioning by the public is interpreted as "bashing," then every group in society today feels bashed. Speak with any patient or friend from any walk of life. Listen to them. You can substitute their professional or business jargon into our litany of "doctor-bashing" quotations, and they sound exactly alike.

Talk to teachers at any level of education from kindergarten to graduate school. They feel unappreciated by society, underpaid for their services, overregulated by government, and blamed for all the ills of society.

Teachers complain of new recredentialing requirements by state and federal agencies that claim they must prove their ability to teach effectively. They grow weary of hearing that the United States spends more of the gross national product on education than any Western power and yet has the worst statistics in achievement scores in mathematics and science, the highest dropout rates, and that many who graduate high school do not have reading and writing skills sufficient to fill out an

employment application. The public is demanding educational reform.

Listen to your friends and patients in banking and commerce: They find a public which is losing confidence in the fundamental strength of the once granite-solid banking system—the foundation of the free-enterprise system. They complain that state and federal regulators have invaded their institutions. They have been forced to hire additional employees just to comply with increasing regulations and have less time to deliver services to their customers. They find profits eroded by the greater demand of insurance funds which protect depositors. They complain of legislation that is allowing everyone to get into the banking business without a license—insurance companies, brokerage firms, automobile manufacturing companies, department stores, and consumer-owned credit unions. The public is demanding banking reform.

Talk to patients and friends in the automobile business. They complain of a public that shows no confidence or respect. They are expected to deliver cars that are perfect and that neither wear nor rust out in spite of a public that drives them recklessly and does not service them properly. Accidents never happen; they are the result of mechanical defects and mechanic failures and should be covered by product liability insurance. Those liability premiums are endangering their ability to stay in business. Very few encourage their children to go into the business. The public demands greater control of the auto industry.

I will not even attempt to invite you to listen to your attorney, patients, and friends. On second thought, perhaps I will. They face a public that ranks them in esteem at record lows, that believes that greed alone motivates them, and that they produce no giants of jurisprudence. Even though lawyers are present in great number in state legislatures, increasing controls on the practice of law emerge in greater number. Recent United States Supreme Court decisions are seen by many as "anti-lawyer." A public that sues at a rate greater than any other country on earth still demands control of the legal profession.

Inaugural address presented before the House of Delegates of the Medical Society of the State of New York, May 1991.

No group is immune. The once untouchable clergy, the Congress of the United States, newspaper reporters, television broadcasters, even the police are the objects of public review and criticism. No one is immune living or dead, including Presidents and Vice Presidents and their first ladies, presidential candidates, governors, mayors, senators, ministers, rabbis, priests, and mullahs. Neither are teachers, lawyers, astronauts, and yes, not even doctors.

I trust my point is clear. We are not alone when it comes to bashing by the public, and we must recognize that this is the start of the public's right to use the tools of the Information Age to measure the performance of its institutions and services. However, there is one place where medicine remains unique in the public view. In the midst of all the public rage against virtually every institution, a recent Gallup Public Opinion Poll ranked physicians high on the list of trusted individuals in society. Ninety-one percent of those polled gave physicians either a very high (9%), high (45%), or average (37%) rating with regard to honesty and ethical standards.¹ The public trust is still there. We are still considered a noble profession.

If we succumb to the insidious malaise and depression that is enveloping us within our profession, we will have no one to blame but ourselves if we lose the public trust we still enjoy. Let us not challenge or resent the public's right to demand of us what they and we are demanding of every other institution—honesty, dignity, fairness, availability, affordability, high quality, and dependability. Let us continue our long-standing efforts to ensure all of these. No other profession has done it for as long as we, and none has done it better.

Let us deliver one more plus, which is our unique professionalism. That unique something that has always set physicians apart from all others in society in every age. That indefinable essence of our profession that makes the title Doctor of Medicine the envy of all. We shall make the case that, because of our professionalism, society can trust us to protect their essential interests as generations of physicians before us have done. That the public does not have to spend tens of millions of dollars on doing what we have done as a profession and can continue to do, if government will just let us do it. Those dollars should be spent on caregiving not caretaking.

Virtually every group in society today seems to be dissuading its young from pursuing their parents' jobs. Perhaps we should review that part of the Oath of Hippocrates which calls on all physicians to teach the Art of Medicine to their children and all who would take that oath. Of all endeavors in life today, none continues to afford the rewards of medical practice, not only monetarily but in those intangibles of public esteem and the fulfillment of knowing that virtually every day offers the opportunity to make a truly significant difference in the lives of so many. I am absolutely convinced that no matter what form medical practice takes in the future, if we maintain the essence of our professionalism, we shall remain among the most respected and best compensated of society.

This is the message we must convey to our young. We have been, we are, and we shall remain the crown jewel

of the professions. We shall convince the public that medicine is a profession that even the recent Harvard Study revealed has a safety and efficiency rate of over 99% and is still striving for 100%.² Not bad for services delivered by mortals.

Society should not be spending 25 cents of every precious health care dollar on the regulatory process when the needs of millions go unfulfilled. To meet these needs, we must be cautious not to destroy the health care system that has produced the greatest medical advances in the history of mankind. We shall press for rational changes that will preserve what is best and improve on what is needed to ensure health care for all.

The Medical Society of the State of New York (MSSNY) will remain in the forefront of this issue. Its Universal Health Plan has received national and state attention. It is one of the major proposals being considered in the Health Access America deliberations of the American Medical Association, as well as by New York State and Federal Officials. The Society has been invited to present its proposal at nine public hearings to be held around New York State this year. We shall not simply react to and protest the programs of others, but will also offer viable initiatives which will help to fashion a rational, affordable, singularly American health care system second to none in the world and with every American included.

We shall challenge our political leadership to cease the irresponsible machinations of state and federal budget-making that deny to our people adequate housing, food, and education, and then fault the health care system for the cost of repairing that human neglect. Good medical care cannot correct those deficiencies. A medically treated homeless person discharged back onto the streets ensures only one thing—that person will surely re-enter the health care system once again to repeat the cycle at great cost to an already beleaguered society.

We shall call for the conversion of now empty mental health facilities, from which many of the homeless where discharged, into housing units with adequate services, which will prevent these repeated, costly re-entries into the health care system. This will certainly be less costly and more humane.

We shall inform the public that programs that prevent teenage pregnancy, drug abuse, domestic violence, environmental pollution, and crime are dollars well spent. Without them the victims of these social problems will enter the health care system at a rate which will doom all cost-cutting measures to abysmal failure.

We shall inform the public that further unreasonable cuts in reimbursement to physicians are bringing the day when access to health care may be seriously jeopardized, if not impossible to deliver. Many physicians with practices that have matured with them are facing the reality that they can no longer economically manage to provide care to their largely Medicaid and Medicare patients. Rather than refuse care to these loyal patients, many physicians are seeking nonpractice alternatives to complete their careers. New physicians considering the assumption of these practices find they cannot even make overhead on current reimbursement rates, yet

alone repay their staggering medical education debts. This reality will be forced home to legislators by efforts of MSSNY and the New York Medical Political Action Committee (NYMPAC).

If our brightest and best find that pursuing the nearly 15 non-income producing years of training after high school and the lifetime commitment to continuing medical education requires that they pauperize themselves and their families, I submit the public will be well advised that the future of medical care may be in grave jeopardy. I believe that an informed public will rally to prevent this for themselves and their children—the future patients and physicians of this country.

MSSNY will persist in its pursuit of medical liability reform. That battle is far from over. We shall press for measures that reduce costs, protect patient interests, and restore rationality to a system that has been totally out of control. Together with the Medical Liability Mutual Insurance Company and NYMPAC, the Society will advance measures on the neurologically impaired

infant issue, oppose pretrial interest payment bills, and seek to protect physicians' personal assets. My colleagues, I am awed by the responsibility and the high privilege of representing you and our profession and ask that you join me in what I call the defense of medical excellence. I have learned so much from so many of you. I pray that you have prepared me well. With your good counsel, your strength, and integrity, together we shall prevail.

CHARLES N. ASWAD, MD
President

Medical Society of the State of New York
420 Lakeville Road
Lake Success, NY 11042

1. Honesty and Ethical Standards, The Gallup Poll, May 22, 1991.
2. *Patients, Doctors and Lawyers. Medical Injury, Malpractice Litigation and Patient Compensation in New York. A Report by the Harvard Medical Practice Study to the State of New York.* Cambridge, Mass, President and Fellows of Harvard College, 1990.

Recommendations for influenza vaccination: From clinical piety to clinical practice

Influenza continues to be an important cause of morbidity and mortality in the United States. It is responsible for an estimated 10,000–40,000 excess deaths¹ and for even greater numbers of excess hospital admissions each year.^{2,3} Its economic impact, measured in current dollars, may approach \$10–\$12 billion annually.⁴ It would seem influenza is a disease well worth preventing. The protective efficacy of influenza vaccine has been demonstrated repeatedly in randomized controlled trials in healthy young adults. Similar clinical trials have never been successfully conducted among elderly populations, and today would not be ethically permissible. Surprisingly, case-control studies of the clinical effectiveness of influenza vaccination have not been reported. Nevertheless, several observational studies have concluded that vaccination is effective for older persons. Thus, for more than 25 years the Immunization Practices Advisory Committee (ACIP) of the US Public Health Service has steadfastly recommended annual influenza vaccination for older persons and for younger persons with high-risk medical conditions.⁵ What has been the result?

If one views only the historical record, our accomplishments have been modest at best. From the late 1960s through 1985, the United States Immunization Survey reported annual vaccination rates of approximately 20% for target populations.⁴ A more recent study suggests that approximately 32% of the elderly are vaccinated each year.⁶ This level falls far short of the goal of vaccinating 60% of the target population set by the Surgeon General in 1980. Furthermore, influenza vaccine distribution over the past decade has not increased; in 1990, only 24 million doses of vaccine were distributed

nationwide, a level similar to those observed as far back as the early 1970s. Given this experience, one might ask whether there are any hopeful signs that things might change. My answer is a cautious yes.

The paper by Buffington and LaForce in this issue of the *Journal* is one of many appearing over the past decade that have focused on issues of influenza vaccine delivery.⁷ The lessons learned from these studies have been remarkably simple but very important. They clearly show that physicians know what they need to know about influenza and influenza vaccination⁴ and that the great majority of high-risk patients will accept influenza vaccine if it is recommended by their physicians.⁸ The fundamental reason why these patients are not vaccinated is that physicians fail to translate their knowledge into clinical practice.^{4,9}

The new knowledge that has emerged has had to do not with what physicians know about “a bad disease and a good vaccine,” but about their vaccination behaviors once they have this knowledge. Physicians have learned that the way to change their behavior is to implement the administrative and organizational changes that ensure that high-risk patients are actually offered influenza vaccine. Whatever the interventions chosen (eg, postcards sent to patients, flags in patient charts, computer-generated reminders to physicians, or importantly, delegation of these tasks to nurses and other healthcare providers), studies undertaken in the outpatient clinics of teaching hospitals have shown that the immunization rates of 60% or greater can often be achieved.⁴ Similar results have been obtained in the setting of a large health-maintenance organization.¹⁰ Recently, Buff-

ington and her colleagues have shown that a target-based model for influenza vaccination can result in a substantial increase in vaccination rates in the office-practice setting.¹¹ Theirs is the first published report that describes influenza vaccination practices in the type of site where most influenza vaccine is given.

An organized approach that is expanded incrementally over a period of several years can result in huge increases in influenza vaccination. This has been impressively demonstrated in a series of studies from the Minneapolis Veterans Affairs Medical Center.¹² Starting with a program that increased vaccination rates for elderly persons in the General Medicine Clinic from 9% to 69% during the period 1983–1986, the program was extended to all 31,000 patients registered in the medical center. The level of influenza vaccine use increased from 600 doses in 1983 to more than 17,000 doses in 1990, and 60% of all elderly patients are now being immunized. (Nichol KL, personal communication) Yet, the numbers of doses of influenza vaccine distributed nationwide have not been changing, suggesting that these demonstrations of effective approaches for vaccine delivery have not been transferred to other settings. Is anything being done to encourage the spread of organized programs for influenza vaccination?

What few readers may realize is that for the past three years the federal government has been engaged in a remarkable program aimed at improving influenza vaccine delivery throughout the United States. In 1987, Congress authorized the Health Care Financing Administration (HCFA) to establish an influenza vaccination demonstration project and appropriated \$25 million per year for up to four years to conduct this project. The legislative history of this program and a critique of its policy goal has been discussed in an earlier publication.¹³ Let me emphasize here, however, what I believe is most important about this project; it represents the first ongoing commitment of federal funds to support adult immunization. For several decades, the Division of Immunization at the Centers for Disease Control has actively collaborated with state and local health officials in childhood immunization programs. These efforts have included bulk purchase of childhood vaccines through a consolidated federal contract and financial support for some of the administrative components of the delivery system. The overall success of this effort cannot be disputed, the resurgence of measles and rubella in certain areas of the country notwithstanding. The HCFA project has begun to do for adults what has worked so well for children.

The HCFA Influenza Vaccination Demonstration Project is now entering its fourth and final year; its authorized support ends September 30, 1992. The goal of the project is to demonstrate the cost-effectiveness of influenza vaccination. If this can be done or if it can at least be shown not to be not cost-effective (a twist of language that says much about the politics of this program), HCFA will be authorized to reimburse physicians and other providers for the cost of influenza vaccine and its administration to Medicare enrollees. Most observers expect this will eventually happen. I

agree that federal reimbursement will be necessary, although I also believe reimbursement alone will not be sufficient to increase influenza vaccination levels dramatically throughout the country. I have two reasons for believing this. First, an identical HCFA reimbursement program for pneumococcal vaccination has had no demonstrable impact on the use of pneumococcal vaccine over the past ten years. Second, during the same ten years, Canada has achieved a three-fold increase in influenza vaccine distribution.¹³ The Canadian approach provides not only reimbursement, but also includes other features similar to the HCFA program, such as government purchase of influenza vaccine and public and provider education.

What will happen when the HCFA project ends on September 30, 1992 is uncertain; 1992–1993 has been called the “gap year” (ie, it is the year after the demonstration project ends but before HCFA issues its report and recommendations). It is possible that valuable momentum might be lost if the project is not extended. None the less, regardless of what happens in the short term, it is my view that eventually we should have active federal support of state and local programs for influenza vaccination and hopefully for pneumococcal vaccination, as well.¹⁴

The studies of Buffington and her colleagues have been conducted under the auspices of the HCFA Influenza Vaccination Demonstration Project and are among the first to be published. These and future studies will provide us with important information on the epidemiology of influenza immunization practices and suggest new ways for physicians to increase their delivery of influenza vaccine to high-risk patients. As a result, the ACIP recommendations on influenza vaccination may become more than yearly exercises in clinical piety; they actually may be translated into effective clinical practice.

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Breaking the chain of HIV transmission

Recent advances in the care of patients with human immunodeficiency virus (HIV) disease have focused on therapeutic modalities to treat the secondary opportunistic infections, as well as on use of azidothymidine (AZT) and other deoxyribonucleoside analogs to try to interfere with the life cycle of HIV.¹ Research on acquired immunodeficiency syndrome (AIDS) vaccines is also being conducted^{2,3} but appears to be much further away from broad clinical application. If therapeutic advances continue at the same relative pace, it seems likely that in the coming decade our ability to keep patients alive longer with HIV infection will continue to improve but that these individuals may not be cured of their infection. If these assumptions prove to be correct, the key to reducing the health burden of HIV into the next century will be in measures to decrease new seroconversions. Particularly in societies where health resources are scarce, the social benefits of HIV disease prevention are likely to be more immediate and profound than those found in HIV therapy.

A part of the process of preventing transmission certainly consists of public education regarding unsafe sexual practices, risks of intravenous drug abuse, and so forth. In those societies where a significant proportion of the women of reproductive age are already infected with HIV, however, even such public education measures will come too late to prevent many cases of vertical transmission. This is likely to be a major part of the burden of HIV disease well into the next century.⁴ Any expenditure now to decrease the risk of vertical HIV transmission would thus not only offer obvious short-term benefits, but would also represent a prudent economic investment in the health of the next generation.

In this context, an important focus for research should be to develop effective and relatively inexpensive strategies to decrease the risk of perinatal transmission of HIV infection. The ideal strategy for intervention to prevent vertical transmission would be to administer therapy before the time of HIV transmission from mother to fetus. This may be a difficult goal to accomplish since Lewis and et al⁵ have reported in a study of aborted fetal tissue from three HIV-infected women that HIV can be detected in the fetus as early as eight weeks of gestational age. Indeed, Lyman and et al⁶ have shown that second trimester abortuses from such women often already have HIV detectable by polymerase chain reaction in the fetal central nervous system.

It is still unclear with what frequency transmission of HIV occurs in early gestation or how efficiently such

transmission produces AIDS in the child. The data presented by Blanche and et al⁷ of the HIV Infection in Newborns French Collaborative Study Group suggest that only about a third of the infants born to HIV-positive mothers will progress to HIV disease. Given that the process of vertical transmission fails on its own in two-thirds of the cases, it seems likely that more effective therapeutic interventions during pregnancy and/or childbirth could further reduce the risk of transmission.

This issue should be readily accessible to investigation in primate models.⁸ Vaccine development trials already require that a large number of primates and other animals be exposed to HIV or its veterinary analogs.⁹ These animals may remain in relatively good health but may no longer be suitable for use in many other sorts of experiments. Retrovirally infected females of reproductive age from among this pool of animals could be used to study measures to reduce vertical transmission. In such an animal model, unlike the human setting, it would be permissible to do fetal blood sampling at serial time points during the pregnancy, even though such fetal blood sampling would carry some risk of hemorrhage and could theoretically increase the rate of maternal-to-fetal transmission.

With the aid of such serial blood sampling, one could investigate whether or not measures during pregnancy such as use of AZT tend to block or delay transmission of HIV to the fetus and evaluate the relative risks and benefits of using drugs that may interfere with DNA metabolism during the various stages of fetal development.

The issue of therapy during pregnancy is less relevant in the case of women who do not present for prenatal care. Routine prenatal care may not be readily available in many of the developing countries where AIDS is of highest prevalence. Even in the industrialized nations where prenatal care is more widely available, many pregnant women with HIV infection, particularly those with major problems such as intravenous drug abuse, may not present themselves to the health care system until they are in active labor.

In these settings, strategies to reduce vertical transmission must focus on the perinatal period. This is a time when fetal organogenesis would have been completed, so that the risk to the fetus of therapeutic interventions may be somewhat less. Nusbaum and Haynes¹⁰ have shown, using an indirect immunofluorescence (rabbit anti-AZT, Incstar; goat anti-rabbit FITC, Sigma) flow

cytometric (Facstar, Becton Dickinson) assay, that AZT is not efficiently incorporated into DNA of the human leukemic cell line HL-60.

Similarly, Huang et al¹¹ have noted that human α - and δ -polymerases do not efficiently incorporate AZT into human DNA. As a result, it seems likely that the DNA of mother and fetus might tolerate a high dose of AZT reasonably well.

A useful therapeutic strategy to explore in this regard would be to treat women with intravenous AZT at the time they go into labor if they are known to be at very high risk of HIV infection. AZT is known to cross the placenta,¹² and this would be an efficient method of giving the fetus a level of AZT before it undergoes the trauma of delivery. The cost of a single dose of AZT should be relatively modest. Even if it produces only a small decrease in the one-in-three estimated risk of vertical transmission, the benefits would be well worth the cost. There is now considerable anecdotal experience with high dose AZT in the form of drug overdoses.¹³⁻¹⁵ It seems clear that a single high dose of AZT would not be expected to produce significant hematologic toxicity. One must be concerned about emesis during delivery either from the childbirth itself or from drug administration, and use of the intravenous route for AZT administration should ensure that good drug levels are obtained in both the mother and the fetus. There have been some reports of neurological toxicity with a high dose of AZT, and so it might be prudent to avoid use of this regimen in deliveries where problems such as pre-eclampsia suggest that either the mother or the child are at a special risk of neurologic complications.

In conclusion, our ability to treat HIV infection is increasing, but a cure is not an early prospect. As a result, AIDS is likely to become a chronic disease in those already infected. The best strategy now for limiting the impact of this disease on succeeding generations is to interfere with further transmission, including vertical transmission. Any measures that can decrease vertical transmission would be a worthwhile expenditure of

health care resources for both the developing and the industrialized countries where AIDS is now a significant problem of women of reproductive age.

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Achievable influenza immunization rates in the elderly

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ABSTRACT. We sought to determine achievable rates of influenza immunization in a large internal medicine practice in which free vaccination was vigorously promoted. A list of 1,230 patients over 65 years of age constituted the target population. Seven hundred ninety patients (64%) were immunized in the office from September to December 1989. In early 1990, questionnaires were sent to 67 patients who had refused vaccination and to an equal number of age- and sex-matched controls who had either accepted the vaccine or whose immunization status was unknown. Seventy-four percent returned the questionnaires. Of the 67 unimmunized patients, 39 (53%) reported that they might be persuaded to accept immunization, whereas 22 (33%) said that nothing could convince them to be immunized. When we added persons who might accept influenza vaccine and persons who had received the vaccine in public clinics to the total number of patients immunized in the office setting, we reached a total of 1,059 patients (86.1% of the total), which we would propose as the maximal achievable immunization rate in this setting.

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In spite of the continued high morbidity and mortality from influenza in the elderly, only about 30% of people over the age of 65 receive yearly immunization against the disease.¹ Several barriers have been hypothesized to account for such poor immunization rates: lack of interest or effort among physicians in promoting vaccination; avoidance, refusal, or lack of awareness on the part of patients to be immunized; and failure of the health care system to pay for the vaccine and its administration.^{2,3} These data have led to an estimated upper limit for immunization rates of 50% to 60% in the elderly.⁴

During the 1989-1990 immunization season, Monroe County, NY participated in a national Medicare Influenza Vaccination Demonstration Project, which provided free vaccination to Medicare recipients and an \$8 administration fee to physicians. In addition, there was extensive public promotion to increase physician and public awareness of the benefits of immunization. We surveyed elderly patients in a large internal medicine practice whose physicians vigorously supported the county-wide project and actively promoted immuniza-

tion. The survey evaluated attitudes about influenza immunization, with the goal of defining a realistic rate of immunization that could be achieved in a private office setting if the cost barrier was eliminated and the vaccine was actively promoted.

PATIENTS AND METHODS

Patients aged 65 years and older were selected from the internal medicine practice of the Genesee Health Service (GHS), a hospital-based practice with seven internists and two medical residents. The practice has a total enrollment of over 24,000 adult patients, with about 2,000 patients aged 65 years and above. Target populations, defined as active patients aged 65 years and older, were enumerated for each physician. Using a simple graphical technique to follow influenza immunizations, performance was quantitated throughout the 1989 immunization season.⁵

Five of the seven physicians in the GHS logged all their patient visits during the immunization period and recorded whether a patient had been vaccinated in the office or had refused. We surveyed the patients who refused the vaccine and a sample of those who had accepted or who had unknown vaccination status.

Of 67 patients recorded as having refused immunization, two were excluded from the study because they were no longer part of the GHS. For each patient who refused, two age- and sex-matched controls were chosen from the same physician's group of patients; one who had accepted immunization ($n = 65$) and one whose immunization status was unknown ($n = 49$). In one physician's practice, 16 patients who refused vaccination could not be matched with patients with unknown vaccine status because too few of his patients fell into this category.

A multiple choice questionnaire was mailed to each of these 179 patients in April 1990. All patients were asked whether they had received an influenza vaccine during the past season, and whether their physician had recommended the vaccine. Patients who reported receiving the vaccine were asked to answer four additional questions: (1) when did they receive the vaccine; (2) where did they receive it; (3) what was the most important reason for getting the vaccine; and (4) had they experienced any side effects. When patients reported not receiving the vaccine, they were asked to answer four different questions: (1) had they ever received an influenza vaccine; (2) had they visited their physician between September 1989 and January 1990; (3) what was the most important reason for not getting the shot; and (4) what, if anything, might convince them to accept immunization in the future. All questions offered multiple choice answers, including "I don't know," and there was ample space for comments.

Cover letters; questionnaires; and stamped, addressed return envelopes were mailed in April. A follow-up letter was mailed, along with a second copy of the questionnaire to nonresponders in early May 1990. Results were coded and entered into a computer program that calculated frequencies of response. χ^2 analysis was used to compare response rates to the question of physician recommendation asked of both groups of patients.⁶ Participants were asked to check one answer to each question; however, in the event that several were checked, a balanced analysis was per-

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formed. For example, if two reasons were cited, they were each given a value of 0.5 in the computations.

RESULTS

Of the 1,230 active patients who were 65 years and over and cared for by these five physicians, 790 (64.2%) were immunized. Another 67 (5.4%) were recorded as having refused the vaccine, and 373 (30.6%) had an immunization status that was unknown. Of 179 questionnaires mailed, eight were returned as undeliverable; 127 of 171 were completed and returned, for a response rate of 74%. There were no statistically significant differences in age, race, or marital status among the three groups of responders. The average age was 74.5 years; data on race were available for 80% of the responders and mirrored the Monroe County distribution: 85% were white; 12% were black; 1.5% were Hispanic; and 1.5% were Asian.

Sixty responders were considered to have been immunized. They included 50 of the initial 54 recorded by the office as having received the influenza vaccine, and 10 of 28 who had originally been in the unknown category but reported having received immunization, presumably in public clinics. The 67 responders in the unimmunized category included 45 patients recorded as "refused" in office data, 18 of 28 patients with an unknown immunization status who reported not receiving immunization, and four patients who had been recorded as being immunized according to office data but who denied receiving the vaccine on the survey.

Of the patients who reported receiving immunization, 86% said that their physicians had recommended it, whereas only 49% of those not receiving the vaccine reported physician recommendation ($p < 0.001$). Fifty-five percent of those immunized cited the doctor's recommendation as the most important reason for accepting immunization (Table I). Twenty-nine percent reported that the severity of clinical influenza was the main reason for accepting immunization, although a few reported that health department recommendations or the availability of free vaccine were determining factors.

Table II summarizes the unimmunized patients' reasons for not getting influenza vaccine. Thirty three (42%) reported either illness from the vaccine in the past or fear of side effects as the main reason for not getting immunized. Approximately 25% listed other reasons, including, "don't get colds or the flu," "leave well enough alone," "don't want it," "don't believe in it," "my immune system is very strong," "no transportation," and no reason listed.

The principal reasons that might convince the 67 unimmunized patients to be vaccinated in the future are shown in Table III. Twenty-two patients (33%) reported that nothing could convince them to accept immunization. However, 21 (29%) reported that they might be convinced by a physician recommendation, and 11 (14%) reported that if they were convinced of the seriousness of influenza, they might consent to be immunized. Seven patients indicated other reasons that might convince them to be immunized.

TABLE I. Principal Reasons for Receiving Influenza Vaccine* (60 vaccinees)

Reason	Responses	
	Number	Percentage
Physician recommendation	38	55
Influenza is a serious disease	21	29
Free immunizations	5	5
Health Department recommendation	4	4
Reports of influenza in the city	4	1
Don't know	2	3
No response	2	3

*Calculations were based on balanced responses, since nine of the 60 responders gave more than one answer to the question.

TABLE II. Principal Reasons for Not Receiving Influenza Vaccine* (67 refusers)

Reason	Responses	
	Number	Percentage
Fear of side effects	18	24
Other [†]	17	23
Illness from shot in past	15	18
No response	7	10
Not offered	7	10
Vaccine not effective in the past	6	6
Don't know	2	3
Allergic to vaccine	2	2
Physician advised against getting vaccine	2	2
Too ill to get vaccine	1	1

*Calculations were based on balanced responses, since seven of the 67 responders gave more than one answer to the question.

[†]See text for details.

nized. Thus, of 67 unimmunized patients, 39 (53%) reported that they might be persuaded to accept immunization.

DISCUSSION

In a setting that favored high rates of vaccine use, physician recommendation was the most commonly reported reason for accepting influenza immunization, whereas fear of side effects or a previous bad experience from the vaccine was the most common reason for not accepting it. Interestingly, more than half of those patients who did not receive the vaccine cited factors that could convince them to be immunized in the future. These findings are consistent with previously published data that describe those who accepted immunization as individuals who sensed that the threat of infection was more serious, that they were more susceptible, and that the vaccine was safer and more efficacious.⁶⁻⁸

Unimmunized patients frequently cited fear of side effects or previous illness from the vaccine. In one study, almost 50% of patients refused immunization in spite of physician promotion because the risks of immunization were perceived to outweigh the benefits.⁴ The investigators theorized that with maximum provider effort, the immunization "ceiling" for influenza vaccine would be 50%-60%. Our data suggest that this is an overly

TABLE III. Reasons That Would Convince Unimmunized to Receive Influenza Vaccine*

Response	Number	Percentage
Nothing would convince	22	33
Physician recommendation	21	29
If convinced of seriousness of influenza	11	14
No response	6	8
Don't know	4	6
Reassurance as to efficacy	3	5
Specific exposure	2	3
Health Department recommendation	1	1
Other	1	1
Availability of free immunization	0	0

*Calculations were based on balanced responses, since four of the 67 responders gave more than one answer.

TABLE IV. Calculation of Achievable Influenza Immunization Rate

Patient Category	Number	Percentage*
Immunized in the practice	790	64.2
Unknown vaccination status (373 patients), among whom 20% were likely to have been immunized	75	6.1
Remaining patients with unknown vaccination status (298 patients), among whom 53% might consent to immunization.	158	12.8
Refused immunization (67 patients), among whom 53% might consent to immunization.	36	2.9
Total achievable immunization	1059	86.1

*Percentage of 1,230 active patients 65 years of age and older in the Genesee Health Service practice.

conservative estimate and that an achievable goal for influenza immunization rates in the elderly is considerably higher.

Using the GHS data, we hypothesize that the vaccination "ceiling" in the elderly is over 80% (Table IV). Ten of 28 responding patients (36%) whose immunization status was unknown by the office indicated that they had received the vaccine. Assuming a higher response rate for patients who accepted the vaccine, a conservative estimate of 20% for the immunization rate in patients whose immunization status was unknown seems reasonable. Using this 20% estimate, an additional 75 patients were probably immunized.

Fifty-three percent of unimmunized patients indicated a factor that could convince them to accept influenza immunization in the future. Among the 298 remaining patients with unknown vaccination status, and the 67 patients who refused immunization, 158 and 36, respectively, would be potential candidates for immunization. Thus, a total of 1,059 (86%) potential vaccine recipients could be identified in the target population of 1,230 persons.

Previous studies have proposed the existence of a group of patients with strong health beliefs, who are unlikely to be influenced by education. A large HMO study using chart-generated reminders reported that 15% of elderly patients refused influenza vaccine when it was offered.⁹ Our study supports the existence of a "hard core" of refusers who are unlikely to be swayed.

Responder bias, patient recall, and reliability are weaknesses inherent in any patient survey study. Our response rate of 74% was regarded as acceptable. Persons who accept health care provider recommenda-

tions may be more likely to complete and return survey questionnaires, and we had no convenient way to evaluate the impact of this potential bias. Four of 54 patients recorded as having accepted vaccination by office staff reported not receiving the vaccine. The remaining responses concurred with office records, giving a reliability of greater than 90%.

A major barrier to achieving high immunization rates remains getting high risk patients to visit their health care providers during each year's immunization season. Encouraging physicians and their office staffs to be more aware of the size of their elderly populations through the use of check lists, and encouraging the elderly to schedule annual visits during the immunization season would help to surmount this barrier.

This study confirms the importance of health benefits in influencing the use of preventive health services. Many elderly persons already believe that the benefits of influenza immunization outweigh the risks, and they readily accept the vaccine. Many others who have not been vaccinated potentially can be persuaded by promotional and educational efforts to receive the vaccine. The results of this study suggest that in office-based practices that eliminate barriers of cost and in which physicians actively promote and offer influenza vaccination, immunization rates greater than 80% should be achievable with the elderly.

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Has the New York State triplicate benzodiazepine prescription regulation influenced sedative-hypnotic overdoses?

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ABSTRACT. A retrospective analysis of sedative-hypnotic overdoses reported to the New York City Poison Control Center (NYCPCC) for the years 1988 and 1989 was performed to evaluate the effects of the triplicate benzodiazepine (BZ) prescription program on the incidence and severity of sedative hypnotic overdoses. Although total BZ overdoses fell slightly, from 1,294 in 1988 to 1,265 in 1989, a statistically significant increase in non-benzodiazepine (NBZ) sedative-hypnotic overdoses, from 111 in 1988 to 144 in 1989, was noted. No difference in clinical outcomes between the two years could be demonstrated. These results suggest that the restriction of BZ failed to reduce the incidence or severity of sedative-hypnotic overdose, largely because of the substitution of similar nonrestricted agents.

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Benzodiazepines are extensively used as muscle relaxants, anxiolytics, sedative-hypnotics, and anticonvulsants.¹ These clinical effects result largely from the ability of BZs to enhance inhibitory neural tone by increasing gamma aminobutyric-acid-mediated chloride conductance across neuronal membranes.² Because of the diversity of indications for BZs, prescriptions for BZs increased in the 1970s at such an alarming rate that "total tranquilization of America" was predicted for the turn of the century.² Although use of BZs has decreased, they remain one of the most commonly prescribed classes of medications. Recent data suggest that as many as 23 million diazepam and 11 million alprazolam prescriptions are written annually.^{2,3} Controversy exists over the extent of the abuse potential and the frequency of misuse and improper prescription of these drugs.⁴ Greenblatt et al¹ cite media sensationalism and "poorly validated and unreliable data bases" as potential sources for this confusion.

BZs were added to the New York State list of schedule II agents on January 1, 1989. This requirement provides that a triplicate form be completed by the

physician for each 30-day supply of medication. One copy of this form is retained by the prescribing physician; the pharmacist retains another and submits the remaining copy to the state. The primary objectives of this program were "to reduce the diversion of these drugs into illicit use and to reduce inappropriate prescribing that can compromise patient well being."⁵

In the calendar year after this legislation, claims for BZs in New York State fell by an estimated 55% for Medicaid, 27% for the Empire Plan (a government employee health plan), and 23% for Elderly Pharmaceutical Insurance Coverage (EPIC).⁵ This may have resulted from the perception by some physicians that the triplicate form hampers their practice by being more time consuming,⁶ rather than an increased awareness of the need to control BZ distribution. Furthermore, the number of prescriptions written might not represent the volume of drug dispensed. Thus, it is unclear as to whether the program's merits should be gauged solely by the number of BZ prescriptions paid for by third-party payers. If the purpose of the program was to reduce diversion of BZ to illicit use and to prevent inappropriate prescribing, might expect the number of overdoses to be reflective of the program's merits.

It is reasonable to expect, however, that cross-tolerant agents would be substituted for BZs in an attempt to circumvent the new regulation. Precedents for this contention exist. An audit was performed comparing prescribing practices before and after the initiation of a triplicate prescription program for schedule II substances in Texas.⁷ The authors of that study noted a significant decrease in prescriptions for those agents classified as schedule II and a significant increase in prescriptions for similar agents that were not placed on the triplicate list.⁷ For example, whereas morphine and codeine prescriptions fell, those for aspirin/codeine and acetaminophen/codeine combinations rose.⁷ Similarly, the creation of a "limited list" in Great Britain resulted in increased prescriptions of available drugs to compensate for the decreased prescribing of others.^{8,9} Notably, when several BZs were "black-listed," prescriptions for the available BZs increased. The total number of BZ prescriptions remained essentially unchanged.

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The purpose of this study was to determine whether the BZ triplicate prescription program has influenced the incidence and severity of sedative-hypnotic overdoses reported to the New York City Poison Control Center. Specifically, the goal of this study was to test the hypothesis that restriction of BZ sedative-hypnotics might result in an increase in overdoses of NBZ sedative-hypnotics.

METHODS

The NYCPCC is a certified Regional Poison Control Center that receives more than 70,000 annual consultation requests. These consults are answered by registered pharmacists who have received specialized training in toxicology; 24-hour physician back-up is available. All consults are routinely entered into a computerized data base.¹⁰ This conforms to requirements for submission to the American Association of Poison Control Centers (AAPCC) National Data Collection System (NDCS). Follow-up data and clinical outcomes are entered within 24 hours of the initial consult and are based on the AAPCC criteria for classification of clinical outcomes. This classification defines clinical outcomes as "none," "minor" (producing mild, non-life-threatening symptoms such as drowsiness or gastrointestinal complaints), "moderate" (producing more significant but transient symptoms such as acid-base disturbances or brief hypotension or seizures), "major" (producing any life threatening symptoms), or "death," on the basis of a specific set of criteria.¹¹

The term "sedative-hypnotic" encompasses a broad variety of pharmacologic agents, including the family of drugs known as BZs. For the purpose of this investigation, sedative-hypnotics were divided into BZ and NBZ sedative-hypnotics. The latter group included chloral hydrate, ethchlorvynol, glutethimide, meprobamate, and methaqualone, exclusively. Barbiturates, antihistamines, and buspirone were not included in the NBZ sedative-hypnotic group because of either varied therapeutic indications (barbiturates), or the lack of cross-tolerance (antihistamines and buspirone) with the sedative-hypnotics.

A retrospective record search of the NYCPCC computer records for 1988 and 1989 was performed to identify all reported ingestions of BZ and NBZ sedative-hypnotics and to determine the clinical outcome of these cases. Consultations involving either a BZ or a NBZ sedative-hypnotic combined with another substance(s) were assigned to their respective groups. Consultations involving both a BZ and a NBZ sedative-hypnotic (< 10 per year) were placed in both groups. In addition, previously published data from the AAPCC NDCS for the five years 1984 through 1988¹²⁻¹⁶ were pooled to provide a data base for comparison. These five years of national data comprise a total of over 5,250,000 overdoses.

A linear regression model¹⁷ was generated from the national data base to develop a predicted incidence of BZ and NBZ sedative-hypnotic overdoses in 1989 for the NYCPCC, on the basis

of 1988 NYCPCC data. The predicted frequency of overdoses was compared with the observed incidence using a χ^2 model.¹⁸ Outcomes of the combined BZ and NBZ sedative-hypnotic groups for 1988 and 1989 were compared using two-way analysis of variance (ANOVA).¹⁹ The linear regression model with Pearson's correlation coefficients, the two-way ANOVA, and the χ^2 analysis were performed on an IBM PC using the Epistat statistical package (Epistat Services, Richardson, TX). Findings with $p < 0.05$ were considered significant.

RESULTS

In 1988, a total of 72,712 consultations were received by the NYCPCC: there were a total of 1,294 BZ overdoses and 111 NBZ sedative-hypnotic overdoses. This compared with a total of 74,048 consultations in 1989; 1,265 of which were BZ overdoses and 144 of which were NBZ sedative-hypnotic overdoses. The distribution of NBZ sedative-hypnotic overdoses for these years are shown in Table I. Assuming that the relative frequency of drug ingestions remained constant over the two years, the 1989 data could be predicted from the 1988 data to increase by 1.84%, which represents the percentage increase in total consults received between the two years. Using this correction, the predicted number of BZ and NBZ sedative-hypnotic overdoses for 1989 would be 1,317 and 113, respectively. A significant difference (χ^2 , $p < 0.05$) was noted between the observed and predicted values. However, because it may not be valid to assume that the incidence of a particular drug overdose is directly related to consult volume, a linear regression model was created to account for changing patterns of drug exposure. The linear regression analysis for the relationship between total overdoses and BZ overdoses predicted an increase of 2.07 BZ overdoses for every increase of 100 total consults ($p < 0.001$, $r = 0.99$). Similarly, for every increase of 100 total consults, an increase of 0.0568 NBZ sedative-hypnotic overdoses was predicted ($p = 0.02$, $r = 0.93$). Thus, for the increase of 1,336 consults received at the NYCPCC in 1989 compared with 1988, this model would predict any increase of 28 BZ and 1 NBZ sedative-hypnotic overdoses. This predicted consult incidence is also listed in Table I. The actual observed incidence of BZ and NBZ sedative-hypnotic overdoses was significantly different from the incidence predicted by linear regression (χ^2 , $p < 0.05$).

The evaluation of clinical outcomes is summarized in Table II. In 1988, in the NBZ sedative-hypnotic group, there were 84, 16, 19, and 0 patients described with none or minor, moderate, severe, and fatal outcomes, respectively. This compares with 113, 19, 10, and 2 for the same respective categories in 1989. Similarly, for BZ overdoses in 1988 there were 1,207, 70, 16, and 1 patient with none or mild, moderate, severe, or fatal outcomes, which compared with 1,198, 49, 15, and 3 patients in 1989 in the same respective categories. Although the numbers of severe and fatal outcomes were too small to permit valid statistical evaluation of individual outcome groups, a two-way ANOVA permits comparison between

TABLE I. Comparison of Actual and Projected Sedative-Hypnotic Overdoses: New York City Poison Control Center

Agent	Overdose Incidence			
	1988 Actual Overdoses	1989 Predicted Overdoses*	1989 Predicted Overdoses†	1989 Actual Overdoses
Benzodiazepines	1,294	1,317‡	1,322‡	1,265
Chloral hydrate	17			27
Ethchlorvynol	38			39
Glutethimide	17			8
Meprobamate	32			64
Methaqualone	7			6
Total non-benzodiazepines	111	113‡	112‡	144
Total sedative-hypnotic overdoses	1,405	1,430	1,434	1,409

*Number of overdoses corrected by telephone call volume.

†Number of overdoses corrected by linear regression model.

‡Significantly different from actual 1989 overdoses (χ^2 , $p < 0.05$).

TABLE II. Clinical Outcomes of Combined Sedative-Hypnotic Overdoses: New York City Poison Control Center

Year	Agent	Outcome Classification			
		None/Minor	Moderate	Major	Death
1988	Benzodiazepines	1,207	70	16	1
	Non-benzodiazepines	84	16	9	0
	Total	1,291	86	25	1
1989	Benzodiazepines	1,198	49	15	3
	Non-benzodiazepines	113	19	10	2
	Total	1,311*	68*	25*	5*

*Not significantly different from 1988 data (Two-way ANOVA, $p > 0.05$).

the two years for the combined clinical outcomes for all categories. The two-way ANOVA showed no significant difference in outcomes in total sedative-hypnotic overdoses for the NYCPCC data for the years 1988 and 1989.

DISCUSSION

These data suggest that both a significant drop in BZ overdoses and a correspondingly significant rise in NBZ sedative-hypnotic overdoses occurred, with total number of overdoses remaining virtually unchanged (1,405 in 1988 vs 1,409 in 1989). The severity of the overdoses did not shift, as judged by the comparison of clinical outcomes between the years before and after the requirement for triplicate forms. Although no significant difference in clinical outcomes could be demonstrated, the increase in deaths in the NBZ sedative-hypnotic group (0 in 1988 vs 2 in 1989) is of concern. The 1988 AAPCC NDCS recorded only five NBZ sedative-hypnotic deaths in an overdose volume more than ten times that of the NYCPCC volume.¹⁶ Pharmacodynamics may help explain these findings; NBZ sedative-hypnotics have lesser therapeutic indices and more significant side effects than BZs. One would expect that any given overdose of a NBZ sedative-hypnotic would be associated with more significant toxicity than any given overdose with a BZ. Because the BZ overdoses represent almost 90% of the total overdoses in the sedative-hypnotic group, this effect might be difficult to demonstrate. However, comparison of the distribution of outcomes in each group of agents (BZ vs NBZ) might be useful. For the combined years 1988 and 1989, there were 2,559 BZ overdoses, of which only 154 (6%) were recorded as moderate, major, or fatal outcomes. There were 255 overdoses in the NBZ group, of which 56 (22%) had similar outcomes. Thus, of overdoses reported to the NYCPCC, the data suggest that NBZ sedative-hypnotic overdoses tended to have more consequential outcomes.

The restriction of BZs therefore may have resulted in the substitution of cross-tolerant drugs with more severe toxicities in overdose. Furthermore, the adverse effects that might result from the routine administration of inferior agents in order to circumvent the triplicate law are equally disconcerting. Finally, one must realize that the triplicate prescription pad is not a panacea for illicit use of schedule II drugs. Troisi et al²⁰ noted that annually, thousands of triplicate pads are reported as stolen, lost, or never received.

The previous American and British experience and our current data suggest that the addition of BZs to the list of schedule II substances has not addressed the

sedative-hypnotic problem as a whole. The problem as we see it is not the absolute number of BZ prescriptions, but rather it is the reasons that the BZs are being prescribed in the first place. A more viable solution might be to restrict the use of all other prescription sedative-hypnotics as well. This would eliminate easy access to substitutes, rather than forcing the use of inferior agents. However, ethanol, which is the most commonly used (and abused) sedative-hypnotic, is available without prescription. Thus, strict control of all prescription sedative-hypnotics might be expected to result in an increase in ethanol consumption.

Finally, several investigators have demonstrated that prescribing practices can be altered by extensive physician and community re-education. Kaufman et al²¹ showed that a 33% reduction in tranquilizer prescriptions (which corresponded to a 52% reduction in total tranquilizer pills) could be achieved after patient and physician education regarding the problem of tranquilizer abuse. Similarly, Manning et al²² noted that peer group educational feedback to physicians concerning their individual prescribing practices resulted in a positive change in 30% of cases. These educational efforts address the underlying problems of substance abuse and improper prescribing practices to improve the overall quality of medical care, rather than attempting to modify physician behavior by restrictive legislation. The authors would like to suggest that greater resources be devoted toward similar efforts.

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MSSNY'S BENZODIAZEPINE INJUNCTION UPHeld Evidence of Abuse "Woefully Scant"

The State Health Department will not be able to force physicians to write prescriptions for benzodiazepines on official New York State triplicate prescription forms quite yet, as an injunction barring the enforcement of the regulation was upheld by the Appellate Division of New York State Supreme Court. MSSNY and other plaintiffs had obtained the injunction initially last fall, but that ruling was appealed by the State Health Department.

The latest decision came on a 3-to-2 vote, Thursday, April 28. Unless the Health Department makes a request to appeal within 30 days, the injunction against enforcement of the benzodiazepine regulation will be in place until the conclusion of MSSNY's suit against the regulation, sometime later this year.

The Court accepted MSSNY's contention that the State Health Department's true motivation in promulgating this regulation was *not* to curb illicit use of benzodiazepines, but rather to "inhibit the use and dispensing of these drugs in New York . . . [and] as a result, Medicaid expenditures in this state would be considerably reduced." In the majority decision, written by Justice Sidney H. Aseh, the Court dismissed Health Commissioner Axelrod's contention of widespread abuse of benzodiazepines by health professionals.

The Health Department's claim "must be viewed in its proper context," said the Court, and noted that Commissioner Axelrod cited only 39 proceedings against health care professionals for improper handling of benzodiazepines. "There are over 50,000 physicians in the State," wrote Justice Aseh, "and, no doubt, at least as many nurses and pharmacists. The purported illicit diversion of benzodiazepines by 39 health care professionals over an unstated period of time . . . is woefully scant evidence of any serious problem."

The justice went on to point out that over 8,000,000 benzodiazepine prescriptions were written in 1985 alone, and flatly stated "it is amazing that the Commissioner can argue that 39 proceedings covering alleged violations for an unstated number of years can be offered as a rational basis for putting a vast number of people in this State under drug abuse surveillance and interfering with the physician-patient relationship of many millions more in the future."

BRIAN QUINN
ELLEN PANZECA, JD
(*The News of New York* 1988; 43:1)

Caroli's Disease

CASE PRESENTATION

John Balian, MD (Resident in Medicine): A 65-year-old man presented at the emergency room of the North Shore University Hospital with right upper quadrant abdominal pain, malaise, and fever of two days duration.

Eleven years prior to admission (PTA), during exploratory laparotomy because of right upper quadrant pain, a liver biopsy was obtained, which revealed diffuse liver hamartomas, focal hepatic fibrosis, and bile duct cysts; a diagnosis of Caroli's disease was made. Since that time, the patient had experienced repeated bouts of cholangitis that had required hospital admission seven years, four years, and one year PTA.

Nine months PTA, after detection of anemia and guaiac-positive stools, a diagnostic evaluation disclosed a gastric mass that was diagnosed as adenocarcinoma and was treated by total gastrectomy. The margins of resection were free of tumor, as were all resected lymph nodes; the patient presented no clinical evidence of recurrence since that time.

Two days PTA, the patient experienced right upper quadrant abdominal pain, malaise, fever to 103°F, anorexia, and darker-than-usual urine. His bowel movements remained regular; he denied dysuria, nausea, vomiting, diarrhea, and jaundice. At the time of admission, the patient's medications included atenolol, aspirin, and trimethoprim-sulfamethoxazole.

The patient's medical history included a Billroth-II resection for peptic ulcer disease in 1949, hypertension of many years duration, resection of benign colonic polyps in 1986, and a myocardial infarction in 1989. He reported allergies to penicillin and intravenous contrast dye. The patient's mother had had gastric cancer.

Physical examination disclosed a 65-year-old man in no distress. His blood pressure was 136/82 mm Hg; respiratory rate, 20/min; and rectal temperature, 37.2°C. The skin and mucous membranes showed no evidence of jaundice or stigmata of liver disease. The lungs were clear to percussion and auscultation. The cardiac point of maximal impulse was not displaced; the first and second heart sounds were normal; a I/VI systolic ejection murmur was audible. The abdomen was mildly to moderately distended; multiple surgical scars were present; the bowel sounds were hyperactive; and the liver percussion span was approximately 12 cm. The right upper quadrant was tender but without muscle

guarding or rebound. Murphy's sign was absent. External hemorrhoids were present; the stool was brown and guaiac-negative; the rectal examination unremarkable. Two-plus pitting edema was present at the ankles; no clubbing, cyanosis, or other abnormalities of the extremities were noted. The neurologic examination indicated mild slowing of mentation but no focal deficits were detected.

The hemoglobin count was 11.9 g/dL, the white blood cell count was 14,500/ μ L, with 88% mature polymorphonuclear leukocytes, 1% immature polymorphonuclear leukocytes, and 11% lymphocytes. The platelet count was 758,000/ μ L; prothrombin time, 13.4 seconds; and partial thromboplastin time, 26.4 seconds. The serum electrolyte levels were as follows: sodium, 137 mmol/L; potassium, 5.2 mmol/L; chloride, 101 mmol/L; bicarbonate, 21 mmol/L; and calcium, 9.4 mg/dL. Blood chemical findings included a blood urea nitrogen (BUN) of 16 mg/dL, creatinine, 1.1 mg/dL; glucose, 82 mg/dL; albumin, 3.7 g/dL; cholesterol, 215 mg/dL; total bilirubin, 1.7 mg/dL (direct 1.5 mg/dL); alkaline phosphatase, 1,231 U/L; lactate dehydrogenase, 2,285 U/L; aspartate aminotransferase (AST/SGOT), 247 U/L; alanine aminotransferase (ALT/SGPT), 202 U/L; and creatine phosphokinase (CPK), 131 U/L.

The electrocardiogram disclosed normal sinus rhythm and a rate of 75/min, with normal wave intervals and axis. The chest film disclosed bilateral blunting of the costophrenic angles and evidence of fibrosis at the right lung base. An abdominal film disclosed no free air in the peritoneal cavity, no evidence of intestinal obstruction, and no air-fluid levels within the bowel.

The presumptive diagnoses on hospital admission were cholangitis and possible metastatic gastric cancer to the liver. On the day of admission, an abdominal sonogram revealed diffuse heterogeneous echoes in the liver, together with evidence of multiple solid nodules. On the sixth hospital day, liver biopsy guided by ultrasound was nondiagnostic. On the eighth hospital day, magnetic resonance imaging (MRI) showed discrete nodules in the liver and possible evidence of the Budd-Chiari syndrome.

In spite of treatment with appropriate fluid management and antibiotics, the patient's hospital course was unfavorable, with progressive deterioration in the liver function, hepatic encephalopathy, and diminishing renal function with the hepatorenal syndrome. On the 15th hospital day, a do-not-resuscitate status was established at the request of the patient's family; he expired later on the same day.

David Cooper, MD, (Assistant Professor of Medicine): With which antibiotics was the patient treated?

Based on a medical conference held at North Shore University Hospital-Cornell University Medical College, Manhasset, NY, on December 4, 1990.

Editor: John Flynn, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

Dr Balian: Broad-spectrum antibiotics were administered from the time of admission but without clinical response. They included cefotetan, 1 g every 12 hours, and gentamicin, 70 mg every eight hours. All cultures of blood and urine were reported negative. As his physical condition and renal function progressively deteriorated, the gentamicin was discontinued, and ceftazidime was substituted for cefotetan.

B. Robert Meyer, MD, (Assistant Professor of Medicine and Pharmacology): How did his symptoms at the time of his final admission compare with those on his earlier admissions for cholangitis?

Dr Balian: The right upper quadrant pain and fever were similar, but the laboratory values were more abnormal on this last admission. Earlier, the alkaline phosphatase level was in the range of 200–300 U/L but was never in the 1,200 U/L range.

Richard Bronzo, MD, (Assistant Professor of Medicine): Did the physical findings on admission indicate the presence of ascites?

Dr Balian: We could not be sure; the findings were equivocal.

Matthew J. McKinley, MD, (Associate Professor of Clinical Medicine; Chief, Division of Gastroenterology): Was the liver biopsy specimen cultured?

Dr Balian: No, if I remember correctly. On pathologic evaluation it presented only nonspecific necrosis.

Dr Cooper: In view of the earlier Billroth-II partial gastrectomy, do you know if a purified protein derivative (PPD) skin test for tuberculosis was done, or whether he was ever given prophylactic isoniazid therapy?

Dr Balian: Not to my knowledge.

Dr Cooper: What about tumor markers on the biopsy specimen or serologic tests for viral hepatitis?

Dr Balian: Tumor markers were not done, as far as I know. The biopsy was not diagnostic. Serologic tests for hepatitis A, B, and C were negative. The level of serum carcinoembryonic antigen was 9.9 U/mL. The Ca 19-9 was elevated at 170 U/ μ L (normal, less than 37 U/ μ L).

RADIOLOGIC PRESENTATION:

Rona Greenberg, MD, (Radiology Resident): The initial computed tomographic (CT) scan at this hospital two years before his final admission demonstrated several small well-circumscribed, low-attenuation lesions in the liver, not diagnostic of but compatible with either simple hepatic cysts filled with serous fluid or with bile duct cysts characteristic of Caroli's disease. To diagnose the latter, we must be able to demonstrate communication of such cysts with the biliary tree,¹ traditionally done by transhepatic cholangiography. Because of the invasive nature of the latter technique, ultrasound and CT have recently been substituted.

Sonographic demonstration of a normal portal radicle within a dilated bile duct is highly suggestive of Caroli's disease.² Similarly, on CT scan, the diagnosis is suggested by the finding of a normal portal tributary filled with contrast medium and surrounded by the low-attenuation image of an ectatic bile duct, the so-called "central dot" sign.³

Ten months PTA, an abdominal ultrasonogram disclosed a fairly homogeneous texture of the liver; the

common bile duct appeared normal; several small cystic lesions were seen in the liver, but no definite communication between the cysts and the biliary tree could be established. Nine months before his final admission, a repeat CT scan without contrast, because of his history of allergy, again disclosed several low-attenuation lesions in the liver, apparently unchanged from earlier examinations. The ultrasound during his final admission disclosed that the gallbladder wall was thickened as much as 4 mm; the liver texture appeared more heterogeneous than on earlier studies; several new nodular masses without cystic characteristics were noted in the liver.

On his final admission, the T-1 weighted image on the MRI disclosed in the liver a heterogeneous signal with foci of increased signal, suggestive of a possible hemorrhagic component. Although limited by respiratory motion, the scan failed to visualize normal hepatic veins, suggesting the further complication of a Budd-Chiari syndrome.

The T-2 weighted images demonstrated marked heterogeneity in the liver, indicating diffuse involvement of the hepatic parenchyma with soft-tissue masses. If these masses were hepatic or bile duct cysts or hemangiomas, the signal on T-2 heavily weighted images should be increased, as we see for the image of the gall bladder. Consequently, the possibility of solid lesions, including neoplasms such as primary hepatoma or cholangiocarcinoma, or metastatic carcinoma from other organs, must be considered. Incidentally, the T-2 weighted scans indicated significant soft-tissue edema.

Dr Bronzo: Did you see evidence of ascites?

Dr Greenberg: Yes, a small amount on the sonogram, but the soft-tissue edema was significant.

Lionel U. Mailloux, MD, (Associate Professor of Clinical Medicine): The hepatorenal syndrome usually occurs in the setting of significant ascites, but the clinical description here does not suggest this. Perhaps the radiologist can tell us about the imaging of the kidneys.

Dr Greenberg: The sonogram demonstrated no hydronephrosis, no evidence of urinary tract obstruction, and no definite evidence of cystic renal disease.

PATHOLOGIC PRESENTATION:

Nafees Pervez, MD, (Attending Pathologist, Long Island Jewish Hospital; Assistant Professor of Pathology, Albert Einstein College of Medicine): The diagnosis of Caroli's disease with congenital hepatic fibrosis and acute cholangitis had been made on the intraoperative wedge biopsy of the liver obtained 11 years PTA. Our current review of the microscopic features of that biopsy indicated not only a preserved lobular architecture, but also many areas of fibrosis containing numerous interlobular bile ducts; cystically dilated bile ducts and acute cholangitis were seen in several portal spaces.

At postmortem examination limited to the abdomen, the peritoneal cavity contained approximately 800 cc of sero-sanguinous fluid. The liver was massively enlarged, weighing 4,000 g, in contrast with the normal weight of 1,400 to 1,600 grams. Sectioning of the liver disclosed a single, large confluent tumor mass occupying the hilum and portions of both lobes, replacing in all about

80%–90% of hepatic parenchyma. The subhepatic vena cava contained a friable, nonocclusive, delicately adherent thrombus; the hepatic veins and their radicles, as well as medium-sized and smaller branches of the portal vein, contained thromboemboli, although the main portal vein did not. The portal, peri-pancreatic, and mesenteric lymph nodes were normal in appearance. No tumor was identified in other abdominal viscera. No residual or recurrent carcinoma was found in the gastric stump, gastric serosa, adjacent lymph nodes, or other tissues.

On microscopic examination, sections from multiple tumor-free areas of the liver confirmed the diagnosis of Caroli's disease with cystically dilated bile ducts (Fig 1). Multiple microhamartomata were present. Although the original pathologic examination of the earlier liver biopsy specimen had suggested congenital hepatic fibrosis, this was not confirmed at autopsy, because many portal spaces were normal in appearance, without fibrosis or increase in interlobular bile ducts.

Caroli's disease is a component of fibropolycystic liver disease and is characterized by congenital, segmental, and saccular dilatation of intrahepatic bile ducts.^{4,6} This rare disorder was first described in 1958 by Jacques Caroli,⁵ and is usually associated with congenital hepatic fibrosis. The condition may overlap with other components of fibropolycystic liver disease, such as polycystic liver and choledochal cysts.

Caroli's disease usually presents in childhood with symptoms of acute cholangitis, major complications include cholelithiasis, amyloidosis, and cholangiocarcinoma.^{4,8} The two unusual features in the present case are its occurrence in adulthood and the absence of congenital hepatic fibrosis.

Histologic study of the hepatic tumor revealed a poorly differentiated adenocarcinoma composed of undifferentiated areas and focal areas with glandular differentiation (Fig 2). The tumor cells were immunoreactive (positive) for a mixture of cytokeratins AE 1-AE 3 but were negative for α -fetoprotein, epithelial membrane antigen, and carcinoembryonic antigen. Both tumor cells and hepatocytes were negative for hepatitis B virus markers; the mucicarmine stains were negative.

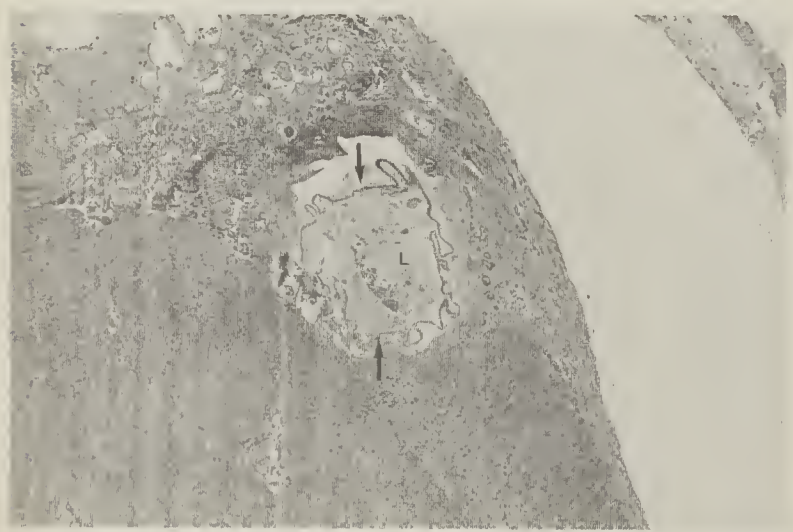


FIGURE 1. Liver biopsy demonstrating Caroli's disease: cystically dilated bile duct (arrows); L, bile duct lumen. (hematoxylin and eosin stain; original magnification $\times 40$)

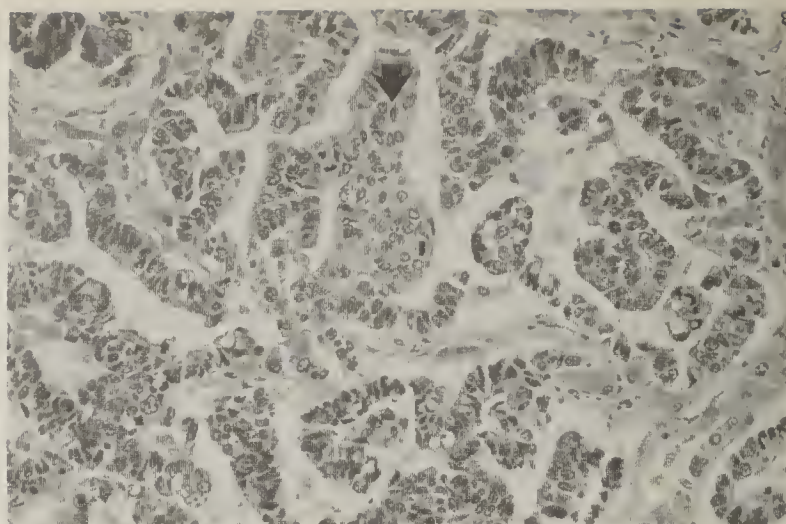


FIGURE 2. Liver at autopsy displays poorly differentiated adenocarcinoma (illustrated at arrow). (hematoxylin and eosin stain; original magnification $\times 200$)

Microscopic examination of the involved blood vessels confirmed the gross impression of tumor thromboemboli in the inferior vena cava and in the hepatic and portal venules. The adjacent hepatic parenchyma showed severe acute, central passive congestion with drop-out of hepatic cells, a pattern compatible with an expression of subacute Budd-Chiari syndrome.⁶

Does the hepatic tumor represent a primary hepatocellular carcinoma, a primary cholangiocarcinoma of bile duct origin, or metastatic gastric carcinoma?

The hematoxylin-eosin and the immunostains allowed us to rule out a hepatocellular carcinoma but did not differentiate between cholangiocarcinoma and gastric carcinoma. The tumor cells in the liver stained positively with cytokeratins AE 1-AE 3; antikeratin AE 1 binds strongly with bile duct epithelium and with the tumor cells of cholangiocarcinoma but not with the keratins of normal liver cells or of hepatocellular carcinoma.⁹

A review of the partial gastrectomy specimen, resected eight months earlier, showed a focally mucus-producing adenocarcinoma with an undifferentiated component not dissimilar to the hepatic neoplasm found at autopsy. Hence, the carcinoma in the liver was compatible with metastatic involvement from the original gastric carcinoma. However, metastatic tumor in the liver commonly presents as multiple nodular masses, whereas single massive confluent metastatic tumor in the liver is distinctly uncommon. In a series of 8,455 adult autopsies, among those with tumor metastasis to the liver, only 6% had a solitary hepatic metastatic mass or nodule.¹⁰

It is well known that Caroli's disease is a risk factor for cholangiocarcinoma, with a frequency range of 2%–14%.^{7,8} Hence, since the carcinoma in the liver is histologically compatible with cholangiocarcinoma, we cannot entirely exclude the possibility that the liver tumor represents a cholangiocarcinoma associated with Caroli's disease.

The kidneys weighed 180 g and 187 g. Cystic disease of the kidneys and medullary ectasia, both known to be associated with fibropolycystic liver disease,^{4,6} were not present in this case. The mild-to-moderate patchy, acute tubular injury observed on microscopic examination

correlated with the clinical picture of acute renal failure. The pancreas and spleen were free of cysts. Recent fibrin thrombi were present in the periprostatic and other pelvic veins and in the inferior hemorrhoidal submucosa vascular plexus, suggesting disseminated coagulopathy.

We can reasonably infer that the patient was in a state of marginal hepatic compensation because of massive replacement of the hepatic parenchyma by carcinoma. The development of subacute and progressive Budd-Chiari syndrome secondary to the vascular spread of tumor thrombi in the inferior vena cava and intrahepatic veins, precipitated overt hepatic failure. Although the postmortem examination was limited, one can conclude that this development was probably the cause of the patient's demise.

Dr Bronzo: In view of the two surgical procedures on the stomach, could you clarify the gastric findings at autopsy?

Dr Pervez: At autopsy, the esophagus was unremarkable. The proximal portion of the stomach was present and was anastomosed, end-to-side, to the jejunum. No ulcerations and no residual or recurrent tumor were found in the gastric stump, in the anastomotic site, or in the adjacent jejunum. The duodenum had a proximal blind end; the ampulla of Vater was patent. The serosa, perigastric tissues, adjacent viscera, and lymph nodes were free of tumor.

CLINICAL DISCUSSION:

David Berger, MD, (Fellow in Gastroenterology): In his original description of Caroli's disease,⁵ Jacques Caroli described patients with segmental cystic dilatations of the intrahepatic bile ducts, with increased incidence of biliary lithiasis, recurrent cholangitis, and liver abscesses, in the absence of portal hypertension and hepatic cirrhosis. The presence of renal tubular cysts was a characteristic feature. This relatively simple form of Caroli's disease is present in a minority of affected patients, whereas the more common periportal fibrosis type presents with the additional features of congenital hepatic fibrosis, portal hypertension, and frequently cysts of the renal collecting system.

The definition of Caroli's disease in the medical literature is quite variable. Some patients are described as having both extrahepatic and intrahepatic bile duct cysts; these various communicating biliary cysts may form a spectrum extending from a predominance of common bile duct cysts to a predominance of intrahepatic cysts. The recent classification by Todani et al¹¹ (Table I) groups together a majority of the patients who have characteristic fusiform common bile duct cysts (Type I cysts), a smaller group as having only intrahepatic cysts (Type 5 cysts), and a third group with both common bile duct cysts and intrahepatic cysts (Type 4A cysts).

Much of the available literature groups together the types 4A and 5; Caroli's original description was confined only to isolated intrahepatic cysts (Todani Type 5). In view of these difficulties and inconsistencies in disease classification, the major texts on liver disease tend to discourage the concept of Caroli's disease as a clinical

TABLE I. Todani Classification of Congenital Bile Duct Cysts

Type I	A. Choledochal cyst B. Segmental choledochal dilation C. Diffuse or cylindrical dilation
Type II	Diverticular type involving whole extrahepatic duct
Type III	Choledochocoele
Type IV	A. Multiple cysts of intra- and extra-hepatic ducts B. Multiple cysts of the extrahepatic ducts only
Type V	Intrahepatic bile duct cyst(s)

entity. Schiff¹² prefers the term "Caroli's syndrome;" Zakim and Boyer¹³ prefer to substitute Todani Type 5 for the condition originally described as the classic Caroli's syndrome.

The symptoms of Caroli's disease are variable¹⁴ and are related mostly to cholangitis, liver abscesses, and biliary stones which are found in approximately one third of patients. In some patients, recurrent cholangitis is marked by fever alone; other patients have recurrent abdominal pain. Hepatomegaly with abnormal liver function tests, particularly with an elevation of serum alkaline phosphatase, may be present, as in this patient. Recurrent bouts of cholangitis may lead to hepatic abscesses—a complication not found in this case.

The majority of patients present with initial symptoms in the first two decades of life, but a significant percentage present in their 50s and 60s. The diagnosis may be made by abdominal ultrasound, with the demonstration of multiple sonolucent spaces; the abdominal CT scan may demonstrate the 'central dot sign' as described by Dr Greenberg.³ Esophageal retrograde cholangiopancreatography (ERCP) may demonstrate the connection between the biliary collecting system and the cysts. Intravenous cholangiography is now rarely used.

In the majority of patients, the disease is diffuse, involving both lobes of the liver. However, in approximately 20% of patients, the disease is monolobar, usually in the left lobe. The complications of this disease are basically the result of stasis of bile and recurrent episodes of cholangitis, both of which contribute to the formation of stones and hepatic abscesses. Extra-hepatic abscesses, septicemia, and secondary amyloidosis have also been described. A 7% incidence of cholangiocarcinoma has been reported,¹⁵ possibly secondary to cholangitis and to the potential tumor-promoting influence of stagnant bile.

In connection with the incidence of cancer, disease classification is important. There appears to be a direct relationship between the cystic changes in the common bile duct and the occurrence of cholangiocarcinoma and other tumors of the hepatic or biliary system, including hepatoma, gall bladder cancer, and pancreatic cancer. Todani et al¹⁶ found in fibropolycystic disease of the liver that 66% of all the cholangiocarcinomas that developed were associated with Type I cysts, 2% with Type 4A cysts involving both common bile duct and intrahepatic cysts, and 6% with Type 5 cysts corresponding to Caroli's disease.

None of the several therapeutic interventions used in Caroli's disease has been satisfactory, including antibiotic therapy to prevent recurrent attacks of cholangitis.

Surgical bypass and choledochojunostomy have been performed for extrahepatic cysts but do not benefit intrahepatic ones.¹⁴ Hepatic resection has been performed in patients with monolobar intrahepatic involvement.¹⁷ Chenodeoxycholic acid and ursodiol may have potential value in altering the lithogenic character of the bile, thereby tending to decrease stone formation.¹⁸ Finally, liver transplantation may be recommended in the diffuse form of the disease with recurrent cholangitis.¹⁴

The variable prognosis in this disease seems to be dictated by the frequency of the attacks of cholangitis, which may be very frequent or may occur at intervals of one to two years.

Dr Meyer: Is there a familial incidence?

Dr Berger: Yes. This is an interesting but confusing aspect of this disease. If you include with this entity polycystic liver disease, which involves noncommunicating bile cysts that contain serous fluid, the condition would be an autosomal dominant disorder. The outcome in that case would be related more to the renal cysts and to renal function. However, Caroli's disease appears to be an autosomal recessive trait.¹⁹

Dr Meyer: The difference then between Caroli's disease and polycystic liver disease is that, in the former, the cysts communicate with the biliary collecting system, and in the latter they do not.

Dr Berger: Correct. In Caroli's disease the hepatic cysts are lined with biliary epithelium.

Dr Meyer: In Caroli's disease, can you clarify the association with renal collecting cysts?

Dr Berger: Renal ectasia is mentioned in the medical literature; 60%–80% of patients with intrahepatic cysts appear to have medullary sponge kidney.¹⁴

Dr Meyer: This patient then represents the minority who do not have that abnormality.

Dr Bronzo: Dilatation of the common bile duct was noted at autopsy in this patient. One of the concerns with Caroli's disease is whether there is some additional common bile duct abnormality that can be associated with an increased risk of cholangiocarcinoma. Were any radiographic studies done on this patient in an effort to demonstrate dilatation of the common bile duct?

Dr Balian: We saw a dilated common duct but did not see a mechanical reason distally for that obstruction. We didn't see tumor in the head of the pancreas, an impacted stone, distal cholangiocarcinoma, or scarring of the common bile duct. So as far as we could tell, there was no distal obstruction.

Dr Meyer: Concerning the issue of gastric carcinoma, there is an association, I believe, between earlier surgery for peptic ulcer disease and the occurrence of subsequent gastric carcinoma. This patient underwent a Billroth-II operation in 1949, and gastric carcinoma developed 30 years later. Would that constitute a valid association?

Dr Berger: It is controversial. It was once more firmly believed that after a Billroth-II operation the patients were at increased risk for the development of gastric stump carcinoma, and some clinicians recommended surveillance studies in order to evaluate this possibility. However, more recent studies are less sanguine about

this association, and currently surveillance is not recommended.²⁰ Anecdotal reports of patients in whom gastric stump carcinoma has developed after a Billroth-II procedure persist in the medical literature. Our policy is not to survey such patients, but at the same time to maintain a low threshold of suspicion concerning any relevant symptoms.

FINAL DIAGNOSIS

Caroli's disease involving the liver, with cystically dilated bile ducts.

Poorly differentiated adenocarcinoma of the liver—possibly cholangiocarcinoma or metastatic gastric adenocarcinoma.

Multiple tumor thromboemboli affecting subhepatic inferior vena cava, hepatic veins, and branches of portal vein.

Severe, acute, central passive congestion in the liver—compatible with subacute Budd-Chiari syndrome.

Multiple microhamartomata of the liver.

Intravascular coagulation in the periprostatic and pelvic veins, and hemorrhoidal vascular plexus—compatible with disseminated intravascular coagulation.

Status-post gastric resection for adenocarcinoma.

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S. Weir Mitchell, Charlotte Perkins Gilman's "The Yellow Wallpaper," and Capgras' syndrome

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It is unusual for a physician still living to be mentioned in a work of fiction, even more so in the critical context that occurs in the short story, "The Yellow Wallpaper."¹ For this reason Charlotte Perkins Gilman's contact with S. Weir Mitchell is of interest, especially because the nature and description of the contact and her feelings about it are available in her autobiography.² It is of additional interest that Gilman's short story incorporates a fascinating description of a variant of Capgras' syndrome, involving an hallucinatory autoscopic double.¹ Some aspects of the protagonist's hallucinations are dynamically related to Gilman's actual contact with Mitchell.

S. WEIR MITCHELL

S. Weir Mitchell (1829–1914) was the most distinguished American neurologist of his time.^{3,4} He was also a neuropsychiatrist and fiction writer whose psychological perceptiveness was best revealed in his novels and short stories, examples of which are *Constance Trescott* and "The Waters of Oblivion."^{5,6,7} Mitchell made his mark as an original investigator when he was a contract surgeon during the Civil War, gaining experience with gunshot wounds and other injuries of nerves.^{8,9} He is known for his descriptions of causalgia, erythromelalgia, and other disabilities, his publications on these themes becoming classics in the history of neurology.⁴ He is also well known in the history of psychiatry for his famous "Rest Cure," long used in its original form and with variations in the United States and abroad.^{10,11}

Mitchell was the brilliant and erudite son of the noted physician, John Kearsley Mitchell, becoming the seventh physician in three generations of medical men. He was born in Philadelphia which remained throughout his life the center of his personal life and medical career. He received his medical degree in 1850 from the Jefferson Medical College.

Mitchell, as physician and writer, conformed to the mores of a highly conservative community. In his short stories and novels, the subtleties of personality functioning and sexual issues were usually revealed indirectly, yet in ways that psychologically minded readers could

fathom. For example, the sexual conflict underlying the development of amnesia in a 19th century British Army officer can be discerned in the aforementioned story, "The Waters of Oblivion."^{6,7} An incest theme can be discerned by perceptive readers in his short novel, *Hephzibah Guinness*, published in 1880.¹² Yet, Mitchell asserted he never wrote anything that might cause a young girl to blush. The Victorian reticence which limited descriptions of feelings and relationships between men and women was evident in much of Mitchell's literary work.^{13,14}

CHARLOTTE PERKINS GILMAN

Charlotte Perkins Gilman (1860–1935) was a lecturer and writer on feminist themes, as well as an author of novels, short stories, and poems. She is best remembered now for her classic, eerie tale, "The Yellow Wallpaper," based on her own severe, depressive episodes.¹ It was published in 1891 in the *New England Magazine*.² Later, it was reprinted in the monthly magazine, *The Forerunner*, which she edited and for which she also wrote.

Gilman was born in Hartford, Connecticut. Unlike Mitchell's family of upper socio-economic class, Gilman's was poor and unstable. Her father abandoned his family, after which they moved 19 times in 18 years.

Gilman's father was a grandson of Lyman Beecher, the theologian, and a nephew of Henry Ward Beecher and Harriet Beecher Stowe, author of *Uncle Tom's Cabin*. At age 24, she married a painter, Charles Walter Stetson, and gave birth to a daughter. Although she regarded her husband as helpful, loving, and considerate, she suffered depressions when at home and improved during periods of separation. They were divorced, and Gilman later married Houghton Gilman, a first cousin and also a descendant of Lyman Beecher. She had left her daughter in the custody of her first husband and fled to California in the wake of continued depression; the divorce and custodial arrangements were scandalous according to the mores of the day.

Gilman was a socialist and early supporter of the labor movement. Lynne Sharon Schwartz, in her introduction to a volume of Gilman's writings, notes that she regarded herself as primarily a sociologist, anthropologist, and social philosopher. Her ideas were radical for her time. Child rearing for example, "she vehemently believed should be entrusted to trained professionals, not

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left to the volatilities of 'maternal instinct'."¹ Schwartz also observed, "She treats the men in her fiction in . . . ambivalent fashion: sometimes as irresponsible, downright dense creatures, occasionally as victims of spiritual asphyxiation."¹

Gilman's views about family and the social scene were delineated in her books which included *Women and Economics: A Study of the Economic Relation Between Men and Women* (1898); *Concerning Children* (1900); *The Home: Its Work and Influence* (1902); *Human Work* (1904); and *The Man-Made World: Our Androcentric Culture* (1911). She also published a Utopian novel, *Herland* (1915). Schwartz also comments in her introduction to Gilman's writings that critics disagree regarding her attitude about sex: "whether she enjoyed it freely, if secretly, or was puritanically repressed or simply uninterested; whether her close women friends were also lovers."

"THE YELLOW WALLPAPER"

The main features of "The Yellow Wallpaper" are given in brief summary here.

A young woman suffers from chronic fatigue and depression. Her husband John, "a physician of high standing," rents a long uninhabited colonial mansion for the summer. His wife says, "There is something strange about the house—I can feel it." She is a writer, but her husband who is "loving" and "takes all care from me," contrary to her wishes, forbids her to work until she is well. She manages to do so surreptitiously. John "hardly lets me stir without special direction." She feels confined and spends much time in her bedroom. "John says if I don't pick up faster he shall send me to Weir Mitchell in the fall, but I don't want to go there at all. I had a friend who was in his hands once, and she says he is just like John and my brother, only more so!" Her brother is also "a physician of high standing."

The woman's bedroom has yellow wallpaper, "repellent, almost revolting." Her husband laughs at her reaction to it. The pattern intrigues her. She begins to observe apparent movement behind it. Gradually and increasingly she hallucinates a "skulking, provoking, formless sort of figure" which eventually assumes the shape of a woman moving behind the wallpaper, its pattern appearing to be bars. The hallucinated figure shakes the bar pattern as if to get out from behind it. At last she creeps into the room. The physician's wife then too begins to creep around the bedroom. She expresses paranoid feelings, even toward her husband. "It does not do to trust people too much." Finally, she merges with the figure behind the wallpaper, her hallucinated autoscopic double.

John is away at work and she decides that on his return, "I want to astonish him." When he appears and sees her, he exclaims, "What is the matter? For God's sake, what are you doing?" His wife then reveals, "I kept on creeping just the same, but I looked at him over my shoulder . . . 'I've got out at last in spite of you . . . and I've pulled off most of the paper, so you can't get me back!'"

The story ends: "Now why should that man have fainted? But he did, and right across my path by the wall, so that I had to creep over him every time!"

MITCHELL'S "REST CURE" AND GILMAN'S AUTOBIOGRAPHY

Gilman wrote in her autobiography about her "increasing depression."^{2(p 87)} She developed a "growing melancholia" involving "every painful mental sensation, shame, fear, remorse, a blind oppressive confusion, utter weakness, a steady brainache that fills the conscious mind with crowding images of distress," remembering "every mistake and misdeeds of a lifetime, and grovels to the earth in abasement." She had the thought, "You did it yourself! You did it yourself! You had health and strength and hope and glorious work before you—and you threw it all away. You were called to serve humanity, and you cannot serve yourself. No good as a wife, no good as a mother, no good at anything. And you did it yourself!"^{2(pp 91-91)}

Gilman decided to seek treatment. "At that time the greatest nerve specialist in the country was Dr S.W. Mitchell of Philadelphia . . . I went to him and took 'the rest cure'; went, with a long letter giving 'the history of the case' in a way a modern psychologist would have appreciated. Dr Mitchell only thought it proved self-conceit. He had a prejudice against the Beechers. 'I've had two women of your blood already,' he told me scornfully. This eminent physician was well versed in two kinds of nervous prostration; that of the business man exhausted from too much work, and the society woman exhausted from too much play. The kind I had was evidently beyond him. But he did reassure me on one point—there was no dementia, he said, only hysteria"^{2(p 95)}.

As for her treatment by Mitchell, Gilman wrote, "I was put to bed and kept there. I was fed, bathed, rubbed, and responded with the vigorous body of twenty-six. As far as he could see there was nothing the matter with me, so after a month of this agreeable treatment he sent me home, with the prescription: 'Live as domestic a life as possible. Have your child with you all the time.' (Be it remarked that if I did but dress the baby it left me shaking and crying—certainly far from a healthy companionship for her, to say nothing of the effect on me.) 'Lie down an hour after each meal. Have but two hours' intellectual life a day. And never touch pen, brush or pencil as long as you live.'"

"I went home, followed these directions rigidly for months, and came perilously near to losing my mind. The mental agony grew so unbearable that I would sit blankly moving my head from side to side—to get out from under the pain. Not physical pain, not the least headache even, just mental torment, and so heavy in its nightmare gloom that it seemed real enough to dodge.

"I made a rag baby, hung it on a doorknob and played with it. I would crawl into remote closets and under beds—to hide from the grinding pressure of that profound distress . . ."

"Finally in the fall of '87 in a moment of clear vision, we agreed to separate, to get a divorce. There was no quarrel, no blame for either one, never an unkind word

between us, unbroken mutual affection—but it seemed plain that if I went crazy it would do my husband no good, and be a deadly injury to my child^{2(p 96)}

"We had been married four years and more. The miserable condition of mind, the darkness, feebleness and gloom, had begun in those difficult years of courtship, had grown rapidly worse after marriage, and was now threatening utter loss; whereas I had repeated proof that the moment I left home I began to recover. It seemed right to give up a mistaken marriage."^{2(p 97)}

Gilman felt both she and her husband had made a mistake by marrying and that their suffering was mutual. She believed that if the decision to divorce had been made sooner, it would have been better for her. "The lasting mental injury would have been less. Such recovery as I have made in forty years, and the work accomplished, seem to show that the fear of insanity was not fulfilled, but the effects of nerve bankruptcy remain to this day."^{2(p 98)} Gilman revealed that throughout her life she suffered recurrent depressions which even her friends were unable to recognize fully. "They see activity, achievement, they do not see the blank months of idleness; nor can they see what the work would have been if the powerful mind I had to begin with had not been broken at twenty-four."^{2(p 98)} Often she was absent-minded and forgetful of people. She neglected invitations, did not answer letters, and had difficulty making decisions.

It is of interest to note that Gilman, during the course of her illness, crawled about and into remote closets and under beds as the woman in "The Yellow Wallpaper" crawled about in her bedroom. She wrote, regarding her story, "It is a description of a case of nervous breakdown beginning something as mine did, and treated as Dr S. Weir Mitchell treated me, with what I considered the inevitable result, progressive insanity."^{2(pp 18-19)} As mentioned earlier, Gilman said the diagnosis in her own case was "hysteria."

Gilman revealed her pointed intention in writing "The Yellow Wallpaper" when she observed, "But the real purpose of the story was to reach Dr S. Weir Mitchell, and convince him of the error of his ways. I sent him a copy as soon as it came out, but got no response. However, many years later, I met someone who knew close friends of Dr Mitchell's who said he had told them that he had changed his treatment of nervous prostration since reading 'The Yellow Wallpaper.' If that is a fact, I have not lived in vain."^{2(p 121)}

Burton Raffel, in his introductory note to Gilman's "The Yellow Wallpaper," which had been included in an anthology he edited, said of S. Weir Mitchell, "His treatment was notably successful."¹⁵ This statement was, of course, made in error, as was evident from Gilman's revelation about recurrent relapses during the course of her life.² In 1935, the same year of publication of her autobiography, Charlotte Perkins Gilman, suffering from breast cancer, committed suicide.

MITCHELL'S OBSERVATIONS ON TREATMENT

The claims made by Gilman about Mitchell and his "rest cure" apparently met with no direct rebuttal by Mitchell. Her allegations and reference to having been

told about Mitchell's modification of his "rest cure" tend to be supported by Mitchell's later comments in an address before the American Neurological Association in Philadelphia on May 21, 1908 and published on June 20, 1908 in *The Journal Of The American Medical Association*.¹⁶ "In January 1874, I developed for a single seemingly hopeless case, literally at a woman's bedside, the treatment by seclusion, rest, massage, full feeding and electricity . . . I do not think of it as a thing mechanically changeless . . . The use of electricity in the future most generally, by agreement, to be left out . . . I said in my book that it was not a necessary adjunct, but that in the rare cases in which massage can not be used electric exercise of the muscles may be of value." Mitchell said he gave up absolute isolation in many cases. "After a while I came to even dispense with rest in bed when the nutrition did not seem to me sufficiently bad to require this measure."

Only guesses are possible regarding the nature of Gilman's contact with Mitchell as she described it, and the consequences of his treatment. For such guesses, one must first assume that Gilman's descriptions were reasonably accurate. Any counterclaims that Mitchell might have voiced are not known. Transference and countertransference ingredients in the therapeutic encounter would surely have influenced its outcome, but any surmise about them now could be too farfetched and therefore unwarranted. One might say that in the Gilman case, Mitchell's treatment was simply one of a number of failures for which the reasons cannot be stated with any measure of certainty. It is probable, however, that the personal backgrounds of the conservative Mitchell and radical Gilman could easily have prompted a clear, unequivocal, and overt clash of personalities, interfering with what might otherwise have been long-term beneficial effects of the "rest cure." This clash was evident at the beginning of their contact when, as Gilman stated in her autobiography, Mitchell felt that her letter supplying her case history was a proof of her "self-conceit." This was followed, as Gilman also alleged, by Mitchell's scornful comment that he had seen "two women of your blood already."

A view might be taken that Mitchell's treatment of Gilman reflected a Victorian attitude toward women just as Victorian conservatism influenced his fiction at that time. One might choose to criticize the authoritarian and repressive approach to treatment by Mitchell in the Gilman case and others, but the authoritarian features in doctor-patient relationships did not preclude beneficial results of treatment for countless patients during and after Victorian times, including the many who apparently benefited by Mitchell's "rest cure." It should be noted that Mitchell, although regarded as an authoritarian figure, was a very good listener. It is known that he was very well liked by many female patients. They confided in him as with no one else. Furthermore, Mitchell said that he learned much from what patients, especially women, did not openly reveal to him as from what they did disclose.^{13,14}

Mitchell's strict and repressive measures for Gilman may have been basically an error in medical judgment when one considers her personality. They resulted in

failure. It has been mentioned, however, that Mitchell eased the requirements that were part of the "rest cure" when he gained experience with the passage of time.¹¹ Gilman herself was aware of this.²

Patients undergoing the "rest cure" were isolated from their customary environment. Thus, they were cut off for a time from influences that might have played a role in the development of their illness. Many of these patients, seeking and getting attention from, and attendance by those close to them, found considerable isolation too confining, and in time were pleased, if not anxious, to return gradually to more normal, prescribed activities. There were others in Mitchell's experience who persisted in demands for a longer bed-ridden existence in spite of his edicts to the contrary. One is reminded of a famous anecdote about the woman who refused to comply with his orders. Mitchell threatened to get into bed with her if she persisted in remaining there. He took off some of his clothes, but she was unmoved. When he started to take off his trousers, however, the very angry woman leaped out of bed, outraged.¹⁴

Mitchell was not only conservative in behavior and in his fiction, but also in his views about limitations in the place and role of women in American society.¹⁴ He was at times seen by colleagues as conceited and pompous. Often dogmatic and authoritarian, he nevertheless did not fail to recognize limitations in results of treatment which no doubt occurred often enough when the "rest cure" was used, as well as in other situations. He stated, for example, "In certain cases of hysteria, insomnia, aphonia, bed cases, simulation of paralysis, a command, an order will sometimes produce abrupt cures. I have at times won these successes. Are they permanent? Rarely. A failure is apt to lessen confidence, and confidence in the physician is a valuable asset. For one success I have had many failures, but of failures we hear too little in the books on psychic treatment."¹⁶

CAPGRAS' SYNDROME AND "THE YELLOW WALLPAPER"

It is worth noting that although Gilman's story "The Yellow Wallpaper" is of interest in reflecting her strong negative feeling about Mitchell's "rest cure," it has additional appeal because of its incorporation of the theme of "a double." The publication of Gilman's story in 1891 preceded by 32 years the clinical account by Capgras and Reboul-Lachaux that centered also on the theme of a "double."^{17,18}

In 1923, Capgras and Reboul-Lachaux described a 53-year-old woman suffering from the delusion that persons significant to her had been replaced by imposters.¹⁸ This type of occurrence was labeled simply Capgras' syndrome in subsequent publications by other clinicians. Most reports of the syndrome appeared at first in British and French psychiatric literature, but many are now published in American journals. A recent study was of a woman who insisted that her visiting sister was in fact a stranger. She had an earlier experience in which she insisted that her husband was an imposter who resembled him.¹⁷

One variant of Capgras' syndrome is the autoscopic type in which patients see doubles of themselves in persons or objects nearby. The woman in Gilman's story saw a double that was both autoscopic and hallucinatory. The syndrome has often been associated with schizophrenia and affective psychoses. Gilman's protagonist deteriorated into a paranoid psychosis. Paranoid schizophrenia has been the diagnosis of patients in a number of clinical case studies of Capgras' syndrome.^{19,20} The syndrome has, in addition, been found in patients with varying types and degrees of brain pathology.²¹

Among proposed psychodynamic theories is one called the "ambivalence theory." This is the most widely accepted. The patient harbors strong ambivalent feelings toward a person significant to him.¹⁷ This ambivalence is clear in the case of the woman in "The Yellow Wallpaper." It involved her relationship with her husband and was reflected in her feelings about his meticulous attention to her, combined with authoritarian repression and control of her activities. The woman's relationship with her husband and Gilman's contact with S. Weir Mitchell are clearly related as Gilman revealed in her autobiography. In the story, the hallucinating woman tells her husband, "I've got out at last in spite of you," and Gilman is apparently, at the same time, telling Mitchell that she got out of the psychological imprisonment in which she felt he had placed her.

A surmise that Gilman knew about the belief in "doubles" is reasonable. People have long been fascinated with the idea of the existence of "doubles." The "doppelgänger" of folklore must surely have been known to this woman with literary, sociological, anthropological, and historical interests.² Especially fascinating, however, is the incorporation of this theme into "The Yellow Wallpaper" which merits attention because of the story's quality and impact. It is a work of fiction now regarded as a classic.

A question arises as to how Gilman came to describe not only a case involving a "double," but specifically a remarkable, eerie depiction of an hallucinatory autoscopic double. The idea might have been a good example of an unusual, imaginative creation by an experienced fiction writer who had not had recourse to any published precedent. One must consider, however, the fact that as a professional writer of fiction, aside from other types of authorship, Gilman almost surely was familiar with earlier publications of internationally renowned writers, and that the works of these master predecessors might well have supplied the nucleus of the autoscopic double central to "The Yellow Wallpaper." Gilman's story, published in the early 1890s was not the first appearance in a literary work of the autoscopic hallucinatory form of Capgras' syndrome.

A recent report notes that an account of an hallucinatory autoscopic double, a variant of Capgras' syndrome, was the major theme in "William Wilson," a story by Edgar Allan Poe published in *Burton's Gentleman's Magazine*, October 1839.^{22,23} This is probably one of the earliest, and perhaps the very earliest description of the phenomenon in a work of fiction by a writer of international fame. Seven years later there appeared Fyodor Dostoyevsky's novel *The Double* about a clerk in govern-

ment service haunted by an hallucinatory autoscopic double.²⁴ The protagonist, Mr Golyadkin, aware of his gradual psychological deterioration, finally lapses into psychosis and is carted off and incarcerated. This tale, longer and more detailed than the Poe and Gilman stories, deserves additional study and evaluation because of its greater psychological complexity and its acclaim as a literary masterpiece.

Although some of the psychodynamics, involving the roles of ambivalence and regression leading to the inexorable lapse into psychosis portrayed in "The Yellow Wallpaper," are readily discernible, the essential features of this story have been presented here in a descriptive fashion while integrating the theme with the Mitchell-Gilman contact and "rest cure" treatment.

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Primary care in New York State: Report and recommendations of the Associated Medical Schools of New York

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Concerns about access to medical care in New York, particularly in the inner city and rural areas, have led to an intensified statewide dialog about the perceived lack of availability of primary care services. In addition to the associated medical schools (AMS), the access issue has been a priority agenda item for the State Council on Graduate Medical Education, the State Legislature, State Departments of Health and Education, New York City Health and Hospitals Corporation, and the Community Service Society of New York. The Council on Health Care Financing also devoted substantial time to it last year.

There are a number of factors contributing to the access problem, but two stand out. The first is the insufficient number of primary care physicians. This concern is documented by the Report of the 1988 Survey of Physicians by the State Education Department, which shows that only 31.6% of New York physicians are in primary care. Moreover, the attractiveness of primary care as a career choice has shown signs of declining even further. In New York, match rates for internal medicine dropped from 90% in 1985 to 78% in 1991, although this reflects in part the significant increase in positions. In the same period, the rates for family practice went from 81% to 65%. The second factor is the statewide geographic maldistribution of physicians, along with the lack of adequate sites for primary care in underserved communities.

AMS is committed to work with state leadership in the public and private sector to (1) encourage student interest in primary care careers, (2) strengthen programs for the education of students and residents in the primary care specialties, (3) introduce medical students to the health care needs of communities, especially disadvantaged communities, and (4) recruit and retain health professionals to work and teach in settings that provide care to underserved populations, both urban and rural.

We recognize that the medical schools have a major responsibility to work with others in strengthening

primary care, and with appropriate support, we are prepared to embrace that responsibility. It must be emphasized, however, that a medical school's central responsibility is to educate students and house staff to achieve their individual highest potential regardless of ultimate career choice. This education should be provided in accordance with the existing and future medical needs of society, and students and residents should be made aware of the environment of medical practice, its opportunities, its challenges and its problems. The choice of career belongs to the student. The responsibility for creating incentives to provide care for all segments of society lies ultimately with society itself and those who govern.

The medical schools will incorporate in their educational mission a determined effort to increase the pool of graduates with a serious interest in primary care. At the same time, the State must work toward the objective of attracting and retaining physicians committed to primary care by addressing the reasons medical school graduates do not select these fields. This task must include development of adequate facilities in which to practice primary care in inner city and rural areas and provision of appropriate financial incentives.

In this report, we use the definition of primary care promulgated by the Institute of Medicine as follows: first contact, continuity, accessibility, comprehensiveness, coordination, and accountability.

There is wide agreement that primary care embraces, at minimum, general internal medicine, general pediatrics, and family medicine. There are strong advocates for the inclusion of other specialties since many physicians, in a broad range of specialties, provide some measure of primary care services, although not necessarily covering all of the above definitions.

It must be emphasized that, although primary care has been the focus of much of the discussion, the real issue is not primary care, per se, but access to comprehensive medical care for all segments of the population.

According to the AAMC survey of medical school alumni who graduated between 1970 and 1979, the percentage of graduates of New York medical schools practicing primary care reflects the national picture. Nationally, 37% of 1970-1979 graduates are in primary

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care, and 36% of New York graduates are primary care physicians. Since approximately 50% of residents in internal medicine in the state do not go on to specialty fellowship training, it is likely that this percentage will increase.

Moreover, the fact that two AMS member institutions are not included in the AAMC data makes the above figures quite conservative. The New York College of Osteopathic Medicine reports that an average of 66% of its last three graduating classes has opted to enter primary care specialties. Although the CUNY Medical School does not offer the MD degree, its emphasis on primary care during the preclinical years has resulted in 73% of its graduates ultimately entering primary care residencies.

The loss of US graduates from primary care residencies has been more than compensated for by the entry of international medical graduates (IMGs) into those positions. Since IMGs who pass the appropriate examinations and complete appropriate training are considered as competent as US graduates, the total numbers of primary care physicians are not inadequate, but their distribution is.

Increasing the numbers of graduates selecting primary care careers represents only one facet of a very complex problem that involves the whole social framework of underserved communities. Key elements in rectifying this include the financing of care for the poor, adequate reimbursement for services, and specific attention by state leaders to such urgent problems as AIDS, substance abuse, and care for the elderly. Other aspects of social structure dysfunction also need concurrent attention.

Given these considerations, only a true partnership among all those with responsibility for the public's health is likely to bear fruit. A major recommendation, then, is the development of a partnership among the State Departments of Education and Health, the Legislature, the Medical Society of the State of New York, the State's hospital associations, and the public and private medical schools. In such a forum, all can discuss how each can exercise their appropriate responsibility in addressing the priority health needs of all New Yorkers. For the medical schools, there is a highly successful precedent for such a partnership in the AMS minority affairs program, in which the resources of the state, the medical schools, and private philanthropy combined to establish the nation's most extensive program to increase the number of minority physicians. AMS has also been working with key legislators to expand and enhance the training and the number of physicians dedicated to the care of the elderly.

THE ROLE OF THE MEDICAL SCHOOLS

It is important to emphasize again that the supply of physicians in this country and in New York is higher than it has ever been and will continue to increase relative to the population. By the year 2,000, it is estimated that there will be 275 physicians per 100,000 people—an increase of 82% from the 1960 ratios. Since the numbers of residency training positions in the surgical specialties have remained fixed or decreased

and the number of fellowship positions continues to decrease, it follows that the total number of physicians in the primary care specialties should increase. However, the urgency of the access and maldistribution problems in the state precludes awaiting this evolution and requires an immediate and active response.

Every medical school in the state has extensive postgraduate training programs in the primary care disciplines and several are enriching their programs even further both to improve the educational process and to encourage interest in primary care. More than half the New York schools have departments of family practice, and all either have required experiences in family practice or extensive experience in the other primary care disciplines and in ambulatory medicine. Many offer experiences in both inner city and/or rural settings. Several engage students in volunteer work with underserved patients or populations.

This constitutes the base from which AMS plans to build its statewide initiative to strengthen the training of primary care physicians. The guiding principle is that the skills and knowledge that characterize primary care physicians are, in fact, essential to all physicians regardless of their specialty. Among these knowledge areas are prevention, psychosocial aspects of medicine, a knowledge of clinical epidemiology, principles and practice of ambulatory care and geriatrics. Some, but not all, of these areas are already part of the required curriculum.

To maximize both effective educational efforts and desired outcomes, four basic issues must be addressed:

1. Commitment by the Dean.
2. Allocation of sufficient curriculum time.
3. Existence of appropriate facilities in which to provide high quality ambulatory training that will attract rather than deter students.
4. A cadre of faculty to serve as role models.

CURRICULUM AND ORGANIZATION

To achieve desired change, the medical schools recognize that they must address several fundamental issues of school organization and operating philosophy. First, AMS supports the GPEP, Macy, and the Larson Committee on Medical Education recommendations, which direct medical schools to develop integrated institutional responsibility through the Dean with centralized authority for curriculum design and management. Once this is done, the commitment to provide students with an appropriate education in primary care throughout the four years of the curriculum can follow.

CLINICAL EDUCATION IN AMBULATORY CARE SITES

In addition to more clinical exposure, including more ambulatory care opportunities during the basic science years, AMS believes that an increasing percentage of students' time during their third year clerkships should also be spent in the primary care disciplines and in ambulatory care sites. We are committed to make an effort to identify appropriate sites both in underserved communities and in locations in which patients from a broad range of socioeconomic groups are served.

Clinical education at ambulatory sites provides opportunities to acquire knowledge, skills, and attitudes that

are essential for the general professional education of physicians, regardless of the ultimate choice of specialty. Compared with acute care inpatient services where the bulk of clinical education is now focused, ambulatory care sites offer more extensive educational opportunities in first contact care, which is fundamental to primary care, in continuity of care, and in important content areas, such as patient-centered interviewing, patient education, prevention, nutrition, clinical epidemiology, occupational medicine, and the management of chronic illness.

In addition, we will explore development of fourth year programs in ambulatory general medicine or pediatrics that would be the outpatient equivalent of the inpatient subinternship. These would balance the time that most fourth year students spend in subspecialty-oriented medical electives, whether outpatient or inpatient. Although residency selections have often already been made by the start of the fourth year, experiences in ambulatory sites during this final year of medical school would reinforce, expand, and sharpen the primary care knowledge and skills for all graduates.

We believe that such experiences can significantly condition students' interest in primary care and career choices, since they are not yet overwhelmed or enticed by the complex, intense, high-tech-oriented specialized experience of the inpatient services of typical tertiary teaching hospitals. Yet, the data suggest that unless this experience is carefully structured in an appropriate educational environment, the effect will be negligible. The AAMC survey of US medical school graduates found that the presence of either a required clerkship or a positive elective experience in family practice had no reported influence on those students in selecting a family practice residency. On the other hand, a recent study at SUNY-Syracuse provided evidence that a third year curriculum with emphasis on primary care positively influenced selection of family practice residencies. Defining an appropriate teaching site and developing a cadre of faculty for ambulatory care is crucial. The use of experienced preceptors, such as office- or health-center-based physicians, is essential, but compensation for lost practice time diverted to education must be considered. Evidence suggests that a physician will experience a 20%—30% loss in efficiency as a result of supervising a medical student. Although supervising residents is less costly, significant incremental overhead costs are associated with all trainees, both students and residents, in these settings. In rural areas, the cost of housing for students is an added factor. Placing students or residents in health centers that serve disadvantaged populations is especially problematic financially because such facilities already suffer from marginal operating revenue and simply cannot absorb the incremental costs of education without some additional public support.

Given the cost factors, AMS recommends that a collaborative effort be made by both the state and the medical schools to set up a sufficient number of ambulatory care sites, under the auspices of the medical school, designed specifically for education. The state's Primary Care Initiative, which is summarized below, may provide an initial step in the development of such practice sites.

Those who have experience in these programs indicate that, among the major determinants of success are strong support from the dean, energetic recruitment of students, good coordination and cooperation between the site and the medical school, and a committed faculty with time to teach.

Another issue is the degree to which clinical training for students and residency training can be integrated to provide a continuum of primary care training. In this regard, the policies of Residency Review Committees, which require that a substantial proportion of training be done in ambulatory sites, become important.

ROLE MODELS

Faculty role models, as noted above, are critical in adding stature to primary care within a medical school. Such role models can be faculty members in medicine and pediatrics, who serve as generalists while making ward rounds or while working in practice-based ambulatory settings. Each of our schools will work within its particular organizational structure to identify and use such individuals and enhance their recognition. The development of strong divisions of General Medicine and General Pediatrics will be important, and we support such initiatives.

THE ROLE OF GOVERNMENT

Without significant changes in the practice environment and the development of greater incentives for primary care, even the best efforts of the medical schools will fall short of the mark. Support is sorely needed in two areas: facilitating, through seed funding, the establishment of ambulatory care environments suitable for teaching students and provision of financial incentives for students to enter primary care and to practice in underserved areas.

For several years, as a way of counteracting the perceived impact of high indebtedness on specialty selection, AMS has advocated the use of loan forgiveness as an incentive for primary care. More recently, several other organizations have made similar recommendations. Loan forgiveness could be extended to all those willing to pursue a primary care practice in an underserved area for a specified length of time. This option remains, in our view, an important one that would address a major barrier to expanding access to primary care. Another state initiative recommended by other organizations and supported by AMS is making loans available for those willing to set up practice in underserved areas.

The state has begun to provide needed resources with its Primary Care Initiative, which has several facets aimed at addressing primary care needs. Among its features are increased Medicaid reimbursement for services to eligible children, insurance coverage for medically indigent children, enhanced reimbursement to free-standing clinics, and funding for hospitals to establish private practices and provide enhanced primary care in underserved communities, including development of practice-based primary care training.

Ironically, the proposed state and federal budgetary reductions for FY92, which will result in immense losses

in hospital revenue, will almost certainly negate this initiative and prevent any new money from being placed in the system. Among programs being severely cut is the budget of the New York City Health and Hospitals Corporation, responsible not only for providing care to vast numbers of indigent people, but also for providing sites for primary care training for six New York City medical schools. Upstate areas will be similarly affected. As a related constraint, the proposed reductions in the SUNY budget and elimination of capitation and reductions in Bundy aid for the private medical schools will essentially cripple most attempts to devote additional medical school resources to initiatives in primary care training.

On the federal level, the potential impact of the Relative Value Scale, which provides comparatively greater reimbursement for time spent in primary care, is unclear at this point.

SUMMARY

Medical education in New York is unique in the country in its scope and its diversity. It is important, as we go forward, that these strengths be neither eroded nor compromised. The AMS member institutions are making a collective commitment to work together to promote changes that will improve medical education for all students by providing them with enriched experience in primary care.

Our major resource is faculty. To whatever degree medical schools can influence career choice, it is essential to this aim that the best possible people are placed in the settings in which primary care is taught. The schools will intensify their efforts to recruit and retain such faculty and, in whatever way is appropriate to each institution, provide them with the stature needed to

emphasize the value which the school places on primary care.

The schools will also work to provide exposure to primary care early in a student's academic career given anecdotal evidence, at least, that such early experience can influence subsequent specialty choice.

Finally, the medical schools will assume greater responsibility for graduate medical education. If, with state support, ambulatory teaching sites are developed, the schools will make every effort to assure that they are staffed with high-quality faculty. Residents and students must see primary care practiced with total commitment to quality.

It is hoped that, with state-initiated improvements in the practice environment, the ultimate outcome will be an increase in the number of our graduates selecting primary care disciplines for their practices and locating in areas in need of physicians. However, to view such an effort by the medical schools as a panacea for the access problems encountered by underserved New Yorkers would be seriously in error. The medical schools are only one component of what must be a comprehensive joint attack on the access problem by both the public and private sectors.

AMS will disseminate these recommendations statewide and will urge a meeting of state leaders to carve out a specific strategy and a timetable. Included in this dialog would be legislators and representatives of the Health and Education Departments and such organizations as MSSNY, HANYS, the Health and Hospitals Corporation, and the Greater New York Hospital Association. We are ready to work with others toward our common objectives, and we call on all of those who share these concerns to participate with us.

Epithelioid sarcoma presenting as lymph node metastasis from an unknown primary lesion

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Epithelioid sarcoma is a rare form of tendosynovial soft tissue tumor exhibiting unique clinical behavior as compared with other soft tissue sarcomas.¹ It is frequently confused with a variety of other neoplastic diseases and was not clearly described until a report of 62 cases by Enzinger² in 1970. The majority of cases involve the extremities. Lymph node metastasis is detected in 30%–50% of patients during the course of the disease.^{3,4} We describe a case of epithelioid sarcoma presenting as a groin mass with no identifiable primary tumor. A review of the literature reveals only one other reported case presenting with lymphadenopathy and an unknown primary site.⁵

CASE REPORT

A 19-year-old female presented to her family physician with an asymptomatic mass in the left groin. She had noted some thickening of the left groin without a discrete mass for approximately one year. The remainder of her medical history was unremarkable.

Physical examination confirmed a mass in the left groin and was otherwise normal. In spite of the course of antibiotics, the mass increased in size. An incisional lymph node biopsy was performed at a local hospital, and the histologic findings were thought to be most consistent with epithelioid sarcoma. Pathologic review at Memorial Sloan-Kettering Cancer Center (MSKCC) disclosed polygonal epithelioid cells with abundant eosinophilic cytoplasm (Fig 1). The nuclei were rounded and vesicular, and spindle cells were occasionally present. Immunohistochemical analysis yielded positive staining for cytokeratins (CAM 5.2) and vimentin. Melanoma and

carcinoma were considered highly unlikely because of negative staining for S-100, HMB-45, AE1, B72.3, Leu-M1, and mucicarmine. Stains for actin and factor VIII were also negative. Both the histologic appearance and the immunohistochemical evaluation strongly supported the diagnosis of epithelioid sarcoma. A computed tomographic (CT) scan of the abdomen and pelvis demonstrated extensive adenopathy of the left groin and slightly enlarged lymph nodes along the left pelvic sidewall.

The patient was admitted to MSKCC for further evaluation. Physical examination at that time revealed hard, matted lymph nodes in the left groin measuring 5 × 8 cm. There were no suspicious cutaneous, subcutaneous, or deep tissue lesions on the left lower extremity or elsewhere. The remainder of the physical was normal. A chest radiograph demonstrated small bilateral pulmonary nodules consistent with vascular and nipple markings but of concern for metastatic disease. Laboratory evaluation was normal with the exception of a slightly elevated lactate dehydrogenase.

We elected to perform a limited laparotomy for staging and a superficial inguinal lymph node dissection for local control of disease in the groin. Exploration through a lower midline incision revealed a small amount of free peritoneal fluid and left iliac, obturator, and para-aortic adenopathy. A hard, 1.5-cm, left para-aortic lymph node was biopsied. After completion of the

abdominal exploration, the matted lymph nodes in the left groin were removed using the standard technique for superficial groin dissection. Pathologic review showed metastatic epithelioid sarcoma in the para-aortic lymph node, and replacing multiple inguinal lymph nodes measuring 3.5–7 cm in diameter. The tumor did not involve subcutaneous tissues or skin. Cytologic evaluation of the peritoneal fluid was negative. The postoperative course was uncomplicated, and the patient was discharged six days after surgery.

A CT of the chest three weeks after surgery revealed multiple small nodules throughout both lung fields and bilateral hilar adenopathy consistent with metastatic disease. Chemotherapy was initiated eight weeks after surgery with doxorubicin hydrochloride and ifosfamide. A near complete response of the pulmonary disease was observed. Follow-up at eight months has not revealed a primary tumor at any site, and there has been continued local control of disease in the groin.

DISCUSSION

Epithelioid sarcoma is uncommon, as judged from our current sarcoma data base of 1,685 admissions from July 1982 to July 1990, which includes only 14 cases. Epithelioid sarcoma usually presents as a single or multinodular subcutaneous mass involving the extremities of young adults.⁶ It is frequently misdiagnosed as squamous cell carcinoma, melanoma, undifferentiated sarcoma, pyogenic granuloma, or necrobiotic granuloma without aid of special studies.^{1,7} It is of interest that atypical mycobacteria (*Mycobacterium marinum*) may be found on microscopic analysis and in bacteriologic culture in granulomatous areas of epithelioid sarcoma, particularly in ulcerated tumors exposed to salt water. Clinical characteristics that distinguish this tumor from other soft tissue sarcomas are its predilection to involve the distal extremities, a high incidence of lymph node metastasis,

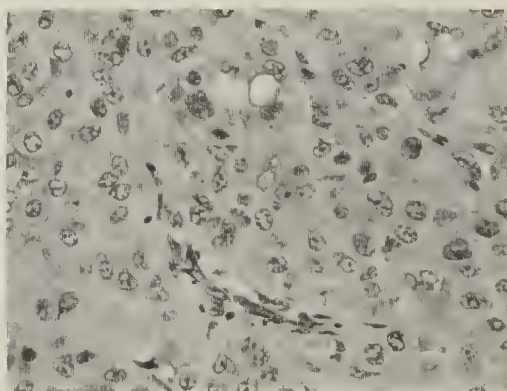


FIGURE 1. Epithelioid sarcoma in an inguinal lymph node. Note the polygonal cells with abundant cytoplasm and rounded vesicular nuclei. (Hematoxylin and eosin stain; original magnification × 100.)

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and a prolonged disease course marked by multiple recurrences that frequently lead to pulmonary metastasis and death.⁶

The majority of epithelioid sarcomas (70%–90%) involve the distal extremities.^{3,4,6,8} The tumor arises superficial to the deep fascia and tends to spread along fascial planes and tendon sheaths. The diagnoses are made by exclusion. Local recurrence after resection is reported in 60%–80% of cases.^{3,4,7} Distant metastasis occurs in about 50% of cases.^{3,4} Whereas lymph node metastasis is uncommon in most extremity sarcomas, 30%–50% of epithelioid sarcomas involve regional lymph nodes either at presentation or during follow-up.^{3,4,6} As observed for all soft tissue sarcomas, more than 90% of patients with lymph node metastasis will die from tumor progression.^{3,6,7}

All cases of epithelioid sarcoma require prolonged follow-up. The mean time from onset of symptoms to death is 7–10 years.^{3,6} Adverse prognostic indicators include multiple recurrences, lymph node metastasis, tumor necrosis, older age, and male sex. Other factors that may be important are tumor site, depth, size, number of mitoses, and presence or absence of vascular invasions.^{3,4,6}

We were able to find only one other case in the literature of epithelioid

sarcoma presenting as lymphadenopathy with an unknown primary tumor.⁵ The patient presented with inguinal lymph node metastasis; a tumor on the foot subsequently developed. Further details of the case, including follow-up, are not provided.

The case we present here demonstrates extensive lymphatic and pulmonary involvement, and the prognosis is in accordance with what has already been described once distant spread has occurred. Although follow-up is less than one year, a primary tumor has not been discovered. The possibility of tumor regression or primary genesis in an inguinal lymph node seems unlikely. The likelihood of a primary lesion arising from the soft tissues of the groin and subsequently invading multiple adjacent lymph nodes is improbable in the absence of a demonstrable focus of extranodal tumor.

Current treatment recommendations for soft tissue sarcomas of the extremities include appropriate limb-sparing resections and adjuvant radiation therapy. The unusual behavior of epithelioid sarcoma suggests that a logical treatment approach may include elective lymph node dissection after treatment of the primary tumor. Data on postoperative radiation therapy of epithelioid sarcoma are sparse. Shimm and Suit¹⁰ reported four of five

patients with limited follow-up alive and free of disease following postoperative irradiation therapy.¹⁰ No meaningful data are available concerning chemotherapy of epithelioid sarcoma. Suggested regimens include doxorubicin hydrochloride, since it remains the most effective single agent for soft tissue sarcomas.

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Spurious neutropenia: Ethylenediaminetetraacetate-dependent in vitro neutrophil agglutination

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Several conditions have been identified that cause spurious granulocytopenia, including leukocyte clumping in the presence of detectable paraproteins,¹ possible destruction of leukocytes by the mechanical and chemical

trauma of automated counting systems in patients with uremia or who are receiving azathioprine and prednisone,² and after excessive disintegration of abnormally fragile white cells, as in chronic lymphocytic leukemia.³ In an isolated case report, spurious granulocytopenia has also been reported to be caused by adherence of platelets to neutrophils in ethylenediaminetetraacetic acid (EDTA) anticoagulated blood.⁴ To our knowledge, there have been no reports of EDTA-

dependent neutrophil agglutination as a cause of spurious granulocytopenia. We present such a case in which spurious granulocytopenia was detected by the identification of white cell aggregates on the blood film prepared with EDTA anticoagulant, but not with other noncalcium chelating anticoagulants.

CASE REPORT

A 37-year-old man was admitted to the psychiatric unit with a diagnosis of unchar-

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acterized schizophrenia. Admission blood work drawn in a vacutainer at room temperature with EDTA anticoagulant revealed a total white cell count of $3,200/\text{mm}^3$ ($3.2 \times 10^9/\text{L}$), with 48% segmented neutrophils, 43% lymphocytes, and 9% monocytes. The hematocrit was 42%, and the platelet count $358,000/\text{mm}^3$ ($358 \times 10^9/\text{L}$). The patient had no significant medical history aside from his schizophrenia; he had not had any surgical procedures or blood transfusions and had no history of recurrent infections. He was on no medication at the time of admission and did not use alcohol or illicit drugs.

The physical examination was unrevealing, and he had normal skin and lacked adenopathy or organomegaly. Blood was redrawn three days after admission into a vacutainer with EDTA at room temperature, and the white cell count was reported as $2,100/\text{mm}^3$ ($2.1 \times 10^9/\text{L}$), with 32% segmented neutrophils and 68% lymphocytes; the hematocrit and platelet count were unchanged as was his general physical condition.

We were then asked to evaluate this patient for neutropenia. Examination of his peripheral smear demonstrated extensive clumping of neutrophils (Fig 1). Repeat complete blood cell counts were performed later the same day on whole venous blood at room temperature using vacutainer tubes with $\text{K}_3\text{-EDTA}$ (1.5 mg/mL whole blood), $\text{Na}_3\text{-citrate}$ (3.8 mg/mL whole blood), Na-heparin (14.3 USP U/mL whole blood), and also with 37°C EDTA and heparin. Blood samples drawn in warm tubes were maintained at 37°C until blood counts were performed. All counts were

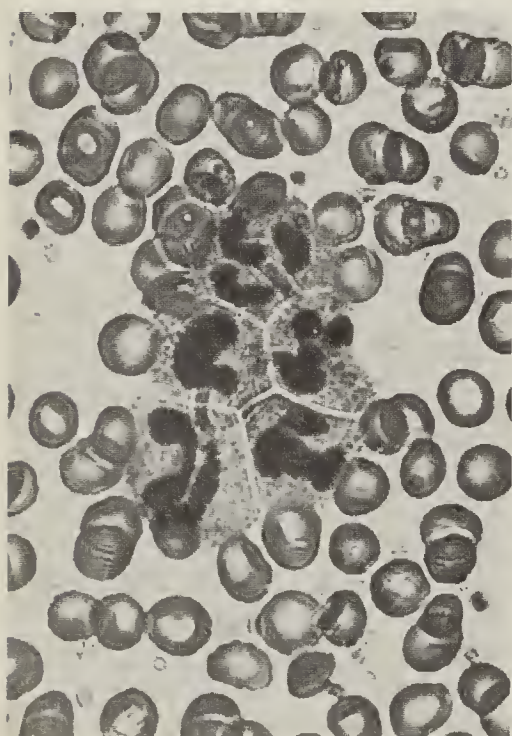


FIGURE 1. Photomicrograph of peripheral blood smear with representative neutrophil clump. (Wright-Giemsa stain, $\times 400$).

TABLE I. Effect of Temperature and Type of Anticoagulant on Blood Counts

	Room Temperature			37°C	
	EDTA	Heparin	Citrate	EDTA	Heparin
Total leukocyte count (cells/ mm^3)	5,300	7,700	7,100*	3,900	7,700
Hematocrit (%)	42	42	38*	42	42

*Not corrected for dilution.

done on Coulter counter Model S (Hialeah, FL). The results are shown in Table I. White cell clumping was not present with the use of either heparin or citrate, and the white cell count was normal with these anticoagulants. Serum protein electrophoresis did not reveal any monoclonal protein, and serum anti-neutrophil antibody testing for IgG and IgM antibodies as well as complement, by previously described techniques, failed to demonstrate white cell antibodies.⁵ The patient was subsequently discharged in good health.

DISCUSSION

EDTA-dependent white cell clumping or agglutination has not been previously described to our knowledge. The mechanism of platelet agglutination in EDTA, however, has been extensively studied and has been found to be a heterogeneous process. In some cases, it is mediated by an IgG antiplatelet antibody independent of calcium, whereas in others the antibody is of IgM class and is calcium ion concentration dependent. It is further hypothesized that chelation and depletion of membrane calcium by EDTA would alter the platelet membrane, revealing neoantigens that would then be the targets of the platelet agglutinins.⁶ The platelet clumping is not mediated by the platelet Fc receptor and requires the presence of membrane glycoprotein IIB/IIIA.⁷

In the case presented here, the white cell counts obtained at room temperature with citrate and heparin anticoagulation were higher than those drawn at 37°C and room temperature in EDTA. Additionally, there was no white blood cell clumping on peripheral blood smears prepared from blood drawn using citrate and heparin. The EDTA leukocyte count at room temperature was higher than with EDTA at 37°C , but no differences in counts were noted at room temperature versus 37°C with heparin. These findings suggest that the clumping observed was not due to a white cell "cold agglutinin." The lower leukocyte count that motivated the initial consultation was obtained by routine processing,

and hence there was a greater delay between blood collection and actual machine counting than for the multiple samples obtained later. The lower initial white cell count suggests that clumping in EDTA was time dependent, however, this variable was not specifically controlled.

In the absence of a previous history of transfusions, it is unlikely that this patient had alloantibodies to neutrophils. Serum antineutrophil antibodies were sought and were not detected. This finding does not exclude the possibility of an EDTA-dependent antibody unique to this patient, since these assays were performed on paraformaldehyde-fixed granulocytes obtained from healthy volunteers. Indeed, as had been described for platelets, in vitro divalent cation chelation by EDTA in this patient may have altered his granulocyte membranes and expressed neoantigens to which the antibodies were then directed.

Automated equipment and particle counters are generally reliable for obtaining blood counts. We have presented this case to alert clinicians to the entity of EDTA-dependent spurious neutropenia. A great deal of further effort and anxiety can be averted in these cases by simple examination of the peripheral blood smear.

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Sesame seed anaphylaxis

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Sesame seed anaphylaxis was first commented on in 1950 by Rubenstein¹ and in 1951 by Uvitsky.² Hypersensitivity to sesame seed was more fully detailed in Torseny's³ description of three cases and has been well described in the literature. The clinical picture and progression of symptoms in these patients is consistent: oral and palatal pruritus, angioedema, urticaria or wheezing, and in some cases hypotension and shock. Systemic anaphylaxis can cause death within minutes. One study showed that the time from antigenic challenge to death varied from 16 to 120 minutes.⁴ Cricothyroidotomy can be life saving; it is relatively easy to perform in an office setting and is effective in cases in which laryngeal edema makes it impossible to intubate the patient.

We present a case of sesame seed anaphylaxis in which a life-saving cricothyroidotomy was performed in an allergist's office. Radioallergosorbent (RAST) scores of sesame seed allergic patients have been reported in cases described by Malish et al⁵; however, the patient described here had a RAST score higher than had been previously described in the literature.

CASE REPORT

A 30-year-old woman with a history of asthma unknowingly ingested a minute amount of sesame seed paste in a salad dressing at a restaurant. She immediately developed a burning sensation in her mouth as well as flushing. She promptly went to her allergist's office just a few blocks away. Within five minutes, she developed generalized itching, urticaria, swelling of the lips and face, protruding tongue, wheezing, and severe respiratory distress. She had a history of penicillin allergy and had previously experienced a burning sensation with swelling of the lips on contact with sesame seed on bread but had never had an anaphylactic reaction.

She was immediately given 0.5 cc of 1:1,000 epinephrine subcutaneously, 50 mg of diphenhydramine, and 8 mg of dexam-

ethasone intramuscularly. Her pulse rate was 140/min, and her blood pressure was not obtained. She had minimal air exchange with bilateral wheezing. She was placed on 100% oxygen by mask, and an additional 0.5 cc of 1:1,000 epinephrine was administered subcutaneously. Because of the rapid onset of respiratory failure, endotracheal intubation was attempted but was unsuccessful because of the laryngeal edema. Cricothyroidotomy was therefore performed. This provided an airway for pulmonary resuscitation; cardiopulmonary resuscitation was begun, during which the patient became cyanotic and had tonic-clonic seizure activity.

She was transported by ambulance to the emergency room, where attempts to intubate her were again unsuccessful. An emergency tracheostomy was done. She was given two more doses of 0.5 cc of 1:10,000 epinephrine and 80 mg of hydrocortisone intravenously, and she was placed on a volume-cycled ventilator. Subsequently, ventricular tachycardia developed, which was controlled with a lidocaine drip (1 mg/cc). Initial arterial blood gas studies on 50% FiO₂ after tracheostomy revealed a pH of 7.03; PaCO₂, 88 mm Hg; PaO₂, mm Hg. Blood gas studies done 30 minutes later on 100% FiO₂, with a respiratory rate of 16 min and a tidal volume of 600 cc showed a pH of 7.42; PaCO₂, 36 mm Hg; PaO₂, 200 mm Hg. Subsequently, her arterial blood gases were well maintained on a respiratory rate of 15/min tidal volume of 600 cc, and FiO₂ of 50%. She was started on hydrocortisone (400 mg every six hours by intravenous drip), aminophylline 6 mg/kg/day intravenously, albuterol (0.5 cc in 3 cc sodium chloride) by nebulizer, ranitidine (150 mg every six hours by intravenous drip), and diphenhydramine (50 mg every six hours intramuscularly).

The next morning, a T-tube was inserted with 40% FiO₂ and was subsequently removed. The facial and oropharyngeal swelling improved significantly by the third day. The patient's temperature rose to 102°F, and the white blood cell count was 27,600 with 68 polymorphonuclear leukocytes, 20 lymphocytes, 10 band forms, and 2 eosinophils. Chest films revealed a left lower lobe infiltrate; *Serratia marcescens* was isolated from the sputum. She was treated intravenously with tobramycin for ten days. Wheezing continued in spite of high doses of corticosteroids and aminophylline.

She was discharged from the hospital after 14 days; bronchodilators and corticosteroids were continued for one month after discharge. A RAST test for sesame seed

done ten days after this exposure revealed a score greater than 17.5 PRU (value was rechecked three times). Her total IgE level by paper radio isorbent test (PRIST) was 130/IU/mL. RAST tests done for other foods including milk, codfish, wheat, and peanuts were not elevated. RAST scores for inhalant antigens (eg, timothy, ragweed, cat and dog epithelium, *Penicillium*, and housedust) were also not elevated. The patient is presently in good health; her tracheostomy wound has healed without complications. She carries an Ana-Kit at all times.

DISCUSSION

Sesame is an herbaceous plant of the Pedalaceae family, of the genus *Sesamum indicum*. It is widely produced in China, Asia, Latin America, and the Middle East. It was never grown extensively in the United States, but it had been grown in the Southeast United States as early as the 17th century by black slaves who brought the seed from their native Africa.⁶

The products of sesame currently marketed are whole seed, extracted oil, and the residual chaff as "meal." The oil is used as salad or cooking oil, in shortening, margarine, cosmetics, perfume, and in some pyrethrum insecticides. The pharmaceutical industry has for many years used it as a vehicle for parenteral injection because of its low antigenicity. The meal is used for cattle and poultry feed.

The whole seed is used as an ingredient of, or in topping for bread, cakes, pastries, and candies. Sesame seed paste called taheen, tahine, tachini, or tahin, depending on the country of origin, may be purchased in cans from many specialty food stores. Some of the sesame seed specialties one may consume at a Middle Eastern restaurant are baba ghanouj (eggplant and sesame paste) and homis di tahini (chickpeas and sesame paste). See Table I for a more complete list of products containing sesame seed.

Sesame oil is used in many restaurants throughout the country, but there have been no reports of hypersensitivity to sesame oil. Torseny³ demonstrated this in two of three patients in a blinded study. Sesame seed, on the

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TABLE I. Common Sources of Sesame Seed and Popular Brand Name Products

Bread, cakes, pastries	FFV Vega Thins, Wheat Thins
Ground seed (almond paste substitute)	Joyva Halva
Sesame seed paste-tahini	Nabisco Cracker Chatter, Sesame Thins, Sociables, Triangle Thins
Sesame paste noodle	Sunshine Biscuit Sesame Cheese, Snack 'n Sesame, Sesame Sticks
Halvah	SS Pierce Sesame Cheese Cocktail Tidbits
Simit (Turkish pretzel)	Chico San Rice Cakes
Sesame wafer and crackers	Golden Harvest Sesame Honey Crunch, Sesame Coconut Crunch
Sesame pretzels	Lifestream Natural Foods, Sunshine Honey Bar
Baba ghanouj (eggplant and sesame seed)	Ghiradelli Chocolate Sesame Bar
Pablano mole sauce (Mexican)	Tania's Sesame Coconut Chews
Sesame hamburger buns	Sahadi Sesame Crunch
Italian bread	Nellson Candies Peanut Butter Sesame Protein Bar
Breadsticks	
Sesame seed bagels	

other hand, is considered to be an extremely potent allergen. The antigenic component in sesame seed extract has a molecular weight of 6,200–8,000 d, thereby indicating that the anaphylaxis-producing substance is a complete antigen and not a hapten.

Systemic anaphylaxis can cause death within minutes. One study of six patients with fatal anaphylaxis demonstrated that the time for antigenic challenge to death varied from 16 to 120 min. Clinical manifestations are variable; they may be very mild initially, yet progress to hypotension, laryngeal edema, bronchospasm, arrhythmia, cardiac arrest, seizures, coma, and death.^{7,8} Shock and death may ensue even without warning signs. Immediate treatment is of the utmost importance and can be life saving.

Molecular structures that can cause anaphylaxis in humans are either complete antigens or haptens. Complete antigens are proteins or polysaccharides, and haptens are low-molecular-weight organic compounds that develop immunogenicity by covalent bonds or, rarely, by ionic linkages. These substances can enter the body by oral, parenteral, topical, or inhaled routes.

The patient showed the classic physiologic changes of anaphylaxis, as evidenced by hypotension and respiratory failure. The recommended emergency treatment of patients with life-threatening anaphylaxis consists of intravenous epinephrine 1:10,000; an H₁ antihistamine, such as parenteral diphenhydramine, 50 mg; an H₂ anti-

histamine, such as intravenous cimetidine, 300 mg or ranitidine.^{7,8} The latter is now generally preferred because of its lack of interaction with other drugs, such as theophylline. Bronchospasm may be treated with intravenous aminophylline, 6mg/kg, and aerosolized β -adrenergic agents.⁷⁻⁹ Steroids can be given in large doses for prevention of late-phase reaction to the offending agent. Intravenous colloids or crystalloids are used for hemodynamic support, and cardiopulmonary resuscitative measures may be indicated. Naloxone, a narcotic antagonist, has been documented to be successful in one case of refractory anaphylaxis,¹⁰ and glucagon has been used in patients on β -blockers who are unresponsive to standard therapy.

RAST, an in vitro assay for specific IgE antibodies, has been in use since 1974.¹ This patient had a RAST score of 17.5 PRU (4+ + +), which is higher than any patient previously recorded. Malish et al⁵ described cases of sesame seed anaphylaxis in which RAST scores ranged from 1+ to 4+, with a mean of 2+. RAST was preferred to skin testing in this case because it required only a simple venipuncture. More importantly, it presented no risk of anaphylaxis to this exquisitely sensitive individual, in whom skin testing was contraindicated.

In this patient, emergency cricothyroidotomy was life saving. The procedure has been described as a "last ditch effort" when other methods fail to secure an airway. This method, sometimes referred to as a "mini-

tracheostomy," provides a route for oxygenation below the edematous larynx. Although the relative ease of this procedure is debatable, the urgency of the situation makes it more desirable than tracheostomy or endotracheal intubation in an office setting.

To perform the cricothyroidotomy, the neck should be hyperextended at an angle of 30–40 degrees. The prominent arch of the thyroid cartilage is then located, and the cricothyroid space is palpated approximately 2–3 finger breadths inferiorly. A large bore needle is inserted until airflow is noted. The major complication of this procedure is laryngeal stenosis, especially if the tube is not converted to a tracheostomy within 24 to 48 hours.¹² There are commercial devices currently marketed for performing this procedure. A layman with no medical background can be taught to use them in a matter of 10–15 minutes.

The hallmark of sesame seed anaphylaxis constitutes a combination of pruritus, urticaria, angioedema, and hypotension. Epinephrine is the drug of choice for the treatment of these reactions. Antihistamines are important adjuncts in gaining further symptom control. Evaluating such patients by RAST testing is safe and may be of special use in cases where skin testing poses the danger of anaphylaxis. Further studies need to be done on the mechanism of reaction to sesame seed. Patients with anaphylactic sensitivity should be taught to self-administer epinephrine. In addition, they should have antihistamines available at all times.

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A congenital müllerian uterine cyst

FARUK AYDIN, MD

Surprisingly, few reports in the recent literature address the issue of uterine cysts.¹⁻⁴ Intramural cysts that arise in the uterus are rare and are classified into two groups, acquired and congenital. The more common and familiar ones are the acquired uterine cysts, including cystic degeneration of myomas⁵ and adenomyomas⁶ cystic endometriosis, cervical retention cysts (nabothian), serosal cysts, and parasitic cysts.⁷ The congenital uterine cysts, which are thought to arise from müllerian or wolffian remnants, are exceedingly rare, and there is little histologic documentation.^{1-4, 8-11} None of the reported cases have had a preoperative correct diagnosis.

A review of the literature from 1850 to the present revealed 47 cases of congenital uterine cysts, most of which appeared in the European literature. Except for three case reports,^{4,11,12} no other report is present in American literature. This paper describes a case of a congenital uterine cysts, with a discussion of the differential diagnosis on clinical and pathologic grounds.

CASE REPORT

A 47-year-old woman, gravida 2, para 2, presented to Beth Israel Medical Center with complaints of menorrhagia and pelvic pain for one year. She also had increased abdominal girth for six months, urgency, and right leg pain and numbness. Her medical history was unremarkable.

On pelvic examination, the cervix was displaced upward. There was an irregular firm mass in the anterior uterine wall. Ultrasonography located a solid mass measuring 13 × 2 cm. The examination of the posterior uterine wall disclosed two separate cystic masses, one of which was felt to be of left adnexal origin. The ultrasonogram showed a complex of left adnexal cystic mass measuring 10 × 9 cm in the

posterior uterine wall. On intravenous pyelogram, this mass appeared to compress the bladder dome and also displaced the sigmoid colon posteriorly, as visualized on barium enema.

On exploratory surgery, the uterus was found to contain one anterior intramural myoma, and another posterior mass, which was felt to be a "cystically degenerated" myoma. The right and left adnexa showed adhesions and a paraovarian cyst. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed.

A vertical section through the posterior uterine wall disclosed a well-circumscribed unilocular cystic structure, 9.5 cm in diameter, which contained a clear serous fluid (Fig 1). The inner surface had a finely wrinkled, gray-pink lining and contained a few coarse intraluminal folds. The cyst wall had a much more trabecular and loosely arranged texture compared to that of the adjacent myometrium. A thorough examination did not reveal any connection of the cyst with adjacent structures. The cyst was entirely confined to the intramural portion of the upper posterior uterine wall and was separated from the endometrial cavity by a myometrial layer of 2.4 cm (Fig 1).

On histopathologic examination, the cyst was lined by a ciliated, tall-columnar epithelium, which also contained scattered dark, intercalated, mucus-secreting cells and "wandering" cells (Fig 2). In a few areas, the epithelia formed papillary and polypoid outgrowths, which contained few glandular structures lined by similar epithelium (Fig 3). The subepithelial areas showed a hypocellular and focally hyalinized stroma reminiscent of the stroma of

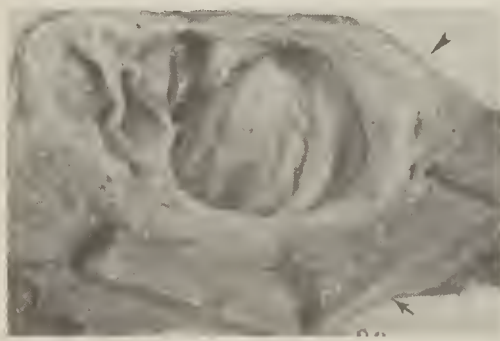


FIGURE 1. The cyst is located very close to the fundic serosal surface (arrowhead). The inner lining is smooth and reveals multiple ridges and trabeculation. The arrow points to the endometrial surface.)

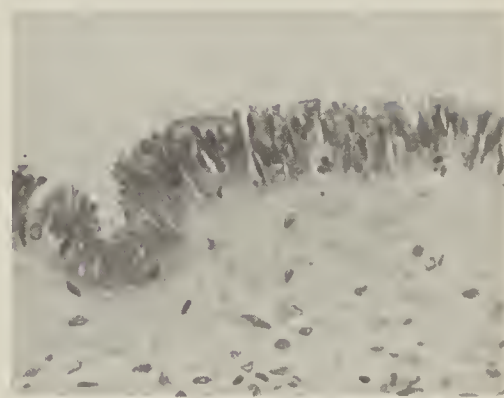


FIGURE 2. The cyst lining consists of ciliated columnar cells, dark intercalated cells, and scattered "wandering" cells. (hematoxylin and eosin stain; original magnification × 424.)

the Fallopian tube. There was no evidence of old hemorrhage, hemosiderin deposition or leiomyomatous changes in the cyst wall.

The left Fallopian tube showed hydrosalpinx formation with occlusion by endometriosis. The left ovary also had a focus of endometriosis and many follicular cysts. The right adnexa were unremarkable.

DISCUSSION

The first case of a congenital uterine cyst was reported by Atlee⁸ in 1850. Subsequent reports mostly appeared in the European literature. Meyer⁹ reviewed 19 cases up to 1930. In the American literature, Sherrick and Vega⁴ reported two cases in 1962, with a review of the previous literature.

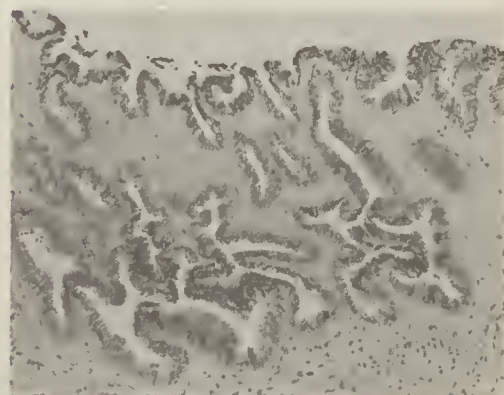


FIGURE 3. The cyst wall shows various glandular structures lined by tubal epithelium. The stroma was partially hyalinized. (hematoxylin and eosin; original magnification × 105.)

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From 1962 to 1991, three more case reports appeared in the European literature.¹⁻³

Sherrick and Vega⁴ defined the histologic diagnostic criteria for congenital intrauterine cysts, which include the following: (1) The cyst should not communicate with the uterine cavity or be lined by endometrium. (2) The cyst should not be connected to endocervical glands, and the lining should differ from endocervical epithelium. (3) The cyst should be located in the myometrium, midline or lateral. (4) The cyst should be lined by cuboidal or columnar epithelium with or without cilia and be either of a low papillary type resembling the paramesonephric duct or of smooth type resembling the mesonephric duct. (5) The cyst wall should be partly composed of myometrium.

By using these criteria, the investigators identified 18 cases of congenital uterine cysts, including their own two. On the basis of the localization of the cyst, they classified 15 midline cysts as paramesonephric (müllerian) and three lateral cysts as mesonephric (wolffian) in origin. The hypothesis that midline uterine cysts are of müllerian origin was originally proposed by Meyer,⁹ who found many examples of müllerian duct remnants in the midline of the fetal uterus. The laterally located uterine cysts, especially below the insertion of the round ligament, are believed to be of wolffian duct origin. Although cysts of wolffian duct origin are rarely described in the uterus, they are more common and are usually located in the paravaginal area. They are lined by mucin-free, typically nonciliated columnar or cuboidal epithelium.

The clinical diagnosis could not be made in any of the reported cases. The

size of the cyst was the only feature relating to symptoms, which ranged from simple pressure to progressive abdominal enlargement simulating myoma or pregnancy. The most frequent preoperative diagnoses were pelvic inflammatory diseases, uterine tumor (myoma or pregnancy), or ovarian versus serosal cyst.

The definitive diagnosis is based on anatomic localization and on histologic findings. Various acquired uterine cystic lesions should be included in the differential diagnosis. Uterine duplication or hydrocolpos can be excluded by demonstration of the communication between the cyst and the uterus. Benign cystic teratoma of the ovary can be distinguished by the presence of ecto- and endodermal elements. Endometrial cysts usually show endometrial stroma with old hemorrhage and endometrial glands. Cystic degeneration in leiomyoma usually not only exhibits a multilocular cystic structure without epithelial lining, but also shows typical features of smooth muscle neoplasm. Cystic adenomyomas may occasionally occur as solitary lesions but usually are associated with a diffuse adenomyosis uteri. The lining epithelium and stroma are typical of the endometrium. Upper endocervical cysts show communication with the endocervical glands and are lined by characteristic endocervical epithelium. Serosal cysts may also mimic congenital uterine cysts. They are derived from mesothelial cells in the uterine serosa. The anatomic location and mesothelial characteristics are distinctive.

The occurrence of congenital uterine cysts should be more common than the literature suggests, because in many reported cases, the size of the cyst was more than 4 cm in diameter. A thor-

ough histologic examination of the uterus may reveal clinically asymptomatic, much smaller cystic structures in the midline or lateral portion of the uterus, which may not have been noticed by conventional radiologic methods. Malignant change in the epithelium of the cyst is also possible, as documented in two cases.⁹ Therefore, a complete histopathologic examination of the uterine cyst will reveal the actual incidence of these lesions and will also rule out malignant transformation.

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Hospital-specific mortality rates for cardiac surgery

TO THE EDITOR: State and Federal Health Agencies are releasing hospital-specific mortality rates for various diagnoses and operative procedures without a full recognition of the harm that is being done through the use of faulty data or the misinterpretation of good data.

A good example was the release of information on hospital-specific mortality rates for cardiac surgery in New York State by the New York State Department of Health reported in the *New York Times* on December 5, 1990 by Lawrence K. Altman and in the *Journal*.^{1,2} These reports compared the mortality rate adjusted for risk for the first six months of 1989 and the first six months of 1990 for the 30 hospitals in New York State performing cardiac surgery. The hospitals were listed in order of increasing adjusted mortality rate, clearly implying that those at the top of the list are superior to those at the bottom.

The methodology used in creating this table was described by Hannan et al,³ who reported New York State data for the first six months of 1989 without identifying specific institutions. These authors reported but did not stress that the data reported for all but four institutions are statistically equivalent at the 95% level of confidence and that one high and one low outlier would be expected on the basis of chance variation alone. Clearly, these are not data that justify an ordered list of mortality rates by specific institution.

The interpretation of these statistics was made even worse by the way in which the data for the two periods were reported in the *New York Times* and the *Journal*. The institution at the bottom of the list, on recommendation of the State Cardiac Advisory Committee, voluntarily performed no cardiac operations for the first four of the six months of 1990, and after reorganization, had only one death during the

two active months. This gave them an erroneously high mortality rate, which was based on only one death in a shorter time period than that used for the other hospitals. If that patient had not died, the institution would have been first on the list rather than the last. Another problem results from the lag time of the information. By the time information has been gathered, analyzed, and reported to the public, major changes may have occurred in cardiac programs, some improving and others deteriorating, making the statistics unrepresentative of the time of publication. In addition, a shift in the time frame used may change the statistics significantly.

It is of interest that none of the data reported in any of these publications was reviewed by the New York State Cardiac Advisory Committee or its Subcommittee on Statistics, which had set up the database and sponsored the research, nor by any of the hospitals before publication. Thus, the data lacked critical review by those most able to do it.

The most important conclusion that could have been drawn from the data was not even mentioned, namely, that over the 30 years for which there are statistics there has been a dramatic reduction in the death rate for these operations in New York State and that the statistics from all of the hospitals in New York State that are approved for cardiac diagnosis and surgery compare favorably with those from others parts of the country. This partly results from the monitoring of cardiac surgery by the New York State Cardiac Advisory Committee.

Reports of this type harm not only hospitals and doctors, but also patients. Hospitals are harmed when unfair statistics are used to compare institutions and to rank them like teams in sports competition. Hannan et al attempted to see if adjusting the death rate for preoperative condition of the patient makes the statistics more comparable.³ The results are

encouraging, although they certainly have not yet proven their superiority or their fairness. A poor statistical showing in such a report most certainly sends patients to other hospitals that in truth may not be superior in performance.

Physicians and surgeons suffer if institutions with which they are associated do not show up well in such imperfect statistics. Not only do they lose patients, but in most institutions it is also possible to identify positively the physicians and surgeons who have been unfairly tainted by the fallacious or incorrectly interpreted statistics.

The greatest losers of all are patients who try to give some meaning to the statistics. Unaware of the problems with statistics, they make decisions based on them. At the very least, the statistics may shake a patient's confidence in the doctors and institutions. Most important, hospitals, physicians, and surgeons may consciously or subconsciously modify the future statistical results by selecting patients for special treatments or operations so that the risks will be minimized. It might therefore be difficult for certain high risk patients to receive optimal treatment. The patient is also harmed when legislators and planning groups, which depend on statistics for making important legislative or planning decisions in the patient's interest, may be led astray by faulty or outdated statistics.

Finally, it should be made clear that we are not advocating the abolition of statistical studies and analyses. We encourage the research that has just begun for establishing data that permit a reliable risk-adjusted mortality rate. We ask that confidence limits be used on the data so that only significant differences among the hospitals are recognized. Hopefully, we will be able to improve our capabilities so that the statistics will have some real meaning and can be reported fairly and responsibly. Until then, we believe that hospital and physician confidenti-

ality should be controlled just as patient confidentiality is controlled.

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The ethics of using scientific data obtained by immoral means

TO THE EDITOR: The conclusion stated at the end of the Committee Report, "The ethics of using scientific data obtained by immoral means," should have been reached even before conferences were held to explore the matter.¹

No data obtained by immoral means can be trusted and the individuals who publish them must be considered liars. They have violated the Oath of Hippocrates by using human subjects for immoral experimental purposes. If those who conduct such research consider the subjects as subhuman, the data obtained should be logically accompanied by the caveat that the findings might not apply to human beings. In any case, such investigators have no credibility and nothing that they publish is reliable.

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Medical abbreviations and acronyms

TO THE EDITOR: Editors of medical journals and textbooks try to make what they publish as readable and as understandable as possible. An article or text littered with many abbreviations may be useful provided their meanings are first defined.

The need for abbreviations is especially great in chemistry and other fields that employ technical phrases. When it is necessary to use such

abbreviations, it is strongly urged that the symbols or abbreviations be spelled out first with the abbreviation immediately following in parenthesis. Thereafter, the abbreviation may be used alone, as for example, angiotensin-converting enzyme (ACE).

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires that to avoid misinterpretations, symbols and abbreviations used in medical records be approved by the medical staff of each hospital. Such lists of authorized symbols and abbreviations must be available to those who make entries in medical records and to those who must interpret them. In addition, each symbol and abbreviation must have only one meaning. When preparing such lists, each hospital should have the input of its health professionals including physicians, pharmacists, nurses, medical record personnel, and all those who make entries in medical records or interpret such information. The need for a *single* meaning for each symbol or abbreviation prevents misinterpretations such as HCT for hematocrit or hydrochlorothiazide or PT for physical therapy or prothrombin time.

In spite of the JCAHO requirement about the use of authorized abbreviations in medical records, their misuse by physicians is rampant. The use of coined acronyms and unauthorized abbreviations has reached such proportions that, in some cases, it is rare for a physician to read a sentence of another physician's progress notes without being unable to decipher unauthorized acronyms or abbreviations.

The intent of the JCAHO is to limit abbreviations with multiple meanings to a single authorized one. The requirement, however, is not being adequately enforced. Close monitoring of medical records is needed to make health professionals conform to this requirement. In some hospitals, abbreviation control officers are designated to monitor medical records for unauthorized abbreviations. Senior clinicians are also asked to inspect clinical records as part of their teaching rounds.

Potential hazards caused by dangerous abbreviations should be brought to the attention of concerned personnel periodically by means of newsletters, hospital memoranda, bulletin boards, or other communication methods.

Some examples of misinterpretation of acronyms include interpreting OD

as the right eye instead of once daily and misreading an order as qh (every hour) instead of as qn (every night).¹

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Editor's comment. Mr. Teplitsky raises an important issue. The use of acronyms without earlier definition of the compound terms they represent is also a continuous problem in medical publishing. It is often done by authors in the mistaken belief that readers will automatically recognize their meanings. However, many acronyms are specialty specific and are unfamiliar to large numbers of readers from other specialty areas. Acronyms should never be used before their meanings are first defined. Once this is done, the acronym should be placed in parenthesis, and thereafter it may be used alone.

PASCAL JAMES IMPERATO, MD
Editor

Scrotal wall edema presenting as the initial manifestation of nephrotic syndrome

TO THE EDITOR: Nephrotic syndrome occurs in approximately one in 50,000 children under 16 years of age.¹ Scrotal wall edema may be the first manifestation of the nephrotic syndrome. The early differentiation from the acute scrotum will avoid an unnecessary surgical exploration.

Case Report. A 3-year-old boy presented with a 24-hour history of painless scrotal swelling. The urology service was consulted to evaluate the acute scrotum. Ten days prior to presentation, the child had symptoms of an upper respiratory tract infection. The genitourinary examination was remarkable for bilateral scrotal wall edema (Fig 1). No appreciable tenderness or erythema was noted. The scrotal wall readily transilluminated. The testes were impalpable secondary to the marked edema.

Mild lower extremity edema was noted. The dipstick of the voided urine in the emergency room revealed 3+ proteinuria. Laboratory studies revealed a specific gravity of 1.035 and 4+ proteinuria on urinalysis. The serum blood urea nitrogen was 14 mg/dL (8-20) and the creatinine was 0.3 mg/dL (0.5-1.4). The sedimentation rate was 37 (0-20). The albumin was 0.9 g/dL (3.5-4.8), the total protein was 3.5



FIGURE 1. The genitourinary examination demonstrates marked bilateral scrotal edema.

g/dL (6.1–8.0) and the cholesterol was 409 mg/dL (140–250).

The child was admitted with the presumptive diagnosis of nephrotic syndrome. He was started on a daily dose of prednisone 2mg/kg/day. A 24-hour urine collection on a 200-cc specimen revealed 2.5 g (0–0.15) of protein. A baseline DTPA renal scan was unremarkable. Scrotal ultrasonography demonstrated bilateral testes and hydroceles (Fig 2). The child was also placed on a sodium-restricted diet, lasix, and 25% albumin. Over a course of six days, the child lost six pounds, the albumin and total protein had risen to 2.0 and 4.9 g/dL, respectively, and the scrotal wall edema was no longer present.

Discussion. Acute scrotal swellings in the pediatric age group demands early evaluation and differentiation of

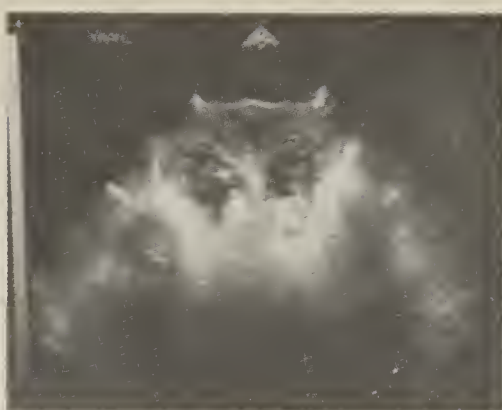


FIGURE 2. Scrotal ultrasonography demonstrates bilateral hydroceles and testes with normal architecture.

those conditions that may be managed conservatively from those mandating surgical intervention. The differential diagnosis of acute scrotal swellings include strangulated hernias, acute hydroceles, torsion of a hernia within the scrotum, idiopathic scrotal edema, torsion of the testis and appendages, traumatic hematoma or hematocele, fat necrosis of the scrotum, acute varicocele, testicular tumor, Henoch-Schonlein purpura, leukemic infiltration of the scrotum, epididymo-orchitis, and scrotal abscess.² Scrotal wall edema may be secondary to an inflammatory process, torsion of the testis or its appendages, or may be a primary process, as in idiopathic scrotal edema.^{3,4}

Nephrotic syndrome is characterized by proteinuria, hypoalbuminemia, edema, and hyperlipidemia. In children under five years of age, the etiology is usually unknown and the entity is designated as idiopathic nephrotic syndrome of childhood. The initial clinical findings may include periorbital swelling and possibly oligu-

ria. Progressive edema leads to overall anasarca and weight gain. Hypertension and pleural effusions may be seen. Additional laboratory studies may demonstrate elevated IgM and low IgG levels. The primary treatment consists of corticosteroids, with supplemental diuretics as needed. Renal biopsy may be indicated in cases unresponsive to steroids or recurrences after an initial response.^{5,6}

Our case demonstrates acute scrotal wall edema as the first manifestation of nephrotic syndrome. The clue to the etiology of the scrotal wall edema was the finding of marked proteinuria. We present this case to illustrate another consideration in the differential diagnosis of acute scrotal swelling and to stress the importance of differentiating this entity from the acute scrotum.

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New York State Department of Health: HIV seroprevalence studies, part II

The following article is the second in a two-part series condensing information from the May 1991 supplement to the American Journal of Public Health, New York State HIV Seroprevalence Project, which summarizes the results of these efforts in New York State. Newborn HIV seroprevalence information was reported in the May 1991 issue of Epidemiology Notes.

HIV seroprevalence data were collected from a number of "windows" in addition to the Newborn Study. The first part of this series reported on information gained from the Newborn Study. This article will focus on geographic and demographic characteristics from the Newborn Study, as well as on information related to the study of female prison inmates, clients of family planning clinics and homeless and runaway adolescents. A summary of projections of AIDS incidence in women is provided in addition to information related to the AIDS epidemic.

Geographic Analysis of Newborn Seroprevalence

Since the AIDS epidemic began, there has been geographic clustering of AIDS cases within the United States and New York State. Most of this clustering is related to prevalence of HIV infection and to risk behavior activities that have been focused in metropolitan areas and states with large at-risk populations (for example, high rate of homosexual/bisexual AIDS cases in New York City, and San Francisco, high rate of intravenous drug use (IVDU) AIDS cases in urban areas of New York, New Jersey and Florida). Initial New York State newborn HIV seroprevalence data have also shown geographic clustering of HIV-seropositive newborns in areas characterized by occurrence of AIDS cases. The HIV-seropositive newborns in New York City also showed clustering in association with IVDU.

The geographic distribution of newborn HIV seroprevalence at zip code level was compared with the distribution of four sociodemographic variables. For New York City, significant univariate correlations were found between HIV and low birthweight, drug use (as measured by hospital discharges), maternal education less than 12 years and race/ethnicity. Less significant correlations were found for New York State exclusive of New York City. For New York City, a model comprising low

birthweight and all drug discharges was shown by multiple regression analysis to be most strongly associated with HIV status ($r = .77$). A model for the rest of the state comprising race/ethnicity (percentage black, percentage Hispanic) and cocaine drug discharges had the best, but less strong association ($r = .39$). However, because of intercorrelations, race/ethnicity added little when the other variables were included first. Knowledge of the geographic association between HIV seroprevalence and sociodemographic status can be useful in designing and focusing prevention efforts in areas at highest risk for future HIV/AIDS activity.

Projections of AIDS Incidence in Women

Data from the Newborn HIV Seroprevalence Study were used with fertility data to estimate the number of HIV-infected women of childbearing age in 1988. The estimate was accomplished for each of 80 age, racial/ethnic, and geographic strata by dividing the number of HIV-seropositive newborns by the 1988 estimated fertility rate. Summing across strata yielded a total of 23,430 infected women ages 15–44 years in 1988. From this estimate, a tree model was used to estimate the number of women infected during 1981–1988. Back calculation was used to distribute the infections over time, and the selected incubation distribution was used to estimate future AIDS cases for this population: 8,295 cases by 1993.

Female Prison Inmates

AIDS is one of the leading medical problems among prison inmates in the United States. In areas where the prevalence of infection with HIV in the general population is high, the problem of AIDS in prisoners is especially acute. New York, which has more reported AIDS cases than any other state, has an especially critical problem with HIV among prisoners.

To determine the prevalence and risk factors for HIV antibodies among prisoners entering the New York State Correctional System, the Department of Health conducted blind seroprevalence studies among consecutive inmates entering the correctional system. Bedford Hills Correctional Facility was the site for testing 480 females entering the system from September through December 1988. Of the 480 women tested, 90 were HIV seropositive (18.8%). The 30–39 age group had the highest seroprevalence; one in four (25%) were positive. Hispanics showed a rate of 29%, which is four times the rate among whites (7%); blacks (14%) showed an intermediate rate between whites and Hispanics. One in four of those with a ninth grade education or less was seropositive.

Of the 136 women who reported a history of IVDU, 45% were HIV positive, compared with 8% of the 339 women who denied IVDU, yielding an odds ratio of 9.4. Nearly 44% of women reporting IV use of heroin without cocaine were seropositive, and over 51% of those using both drugs intravenously tested positive.

Women who reported having had sex with an IV drug user showed a seroprevalence rate of 38%, compared with 14% for women denying this risk factor.

Sentinel Family Planning Clinics

The purpose of studying sentinel family planning clinic clients was to document the prevalence of HIV antibody in women attending the clinics throughout New York State and to monitor trends in infection over time.

Between February 1, 1988, and March 31, 1990, 27,549 specimens were available for HIV serologic testing. Of these, 144 (0.52%) were HIV-antibody positive. The highest rates were detected in residents of New York City (0.82% seroprevalence). The seroprevalence rate for residents living in other parts of the state was 0.24%. No seropositives were detected among the 805 individuals tested under the age of 15, and only three seropositives were detected among the 805 individuals tested under the age of 15, and only three seropositives were detected among the 722 individuals age 40 or more. The trend of increasing seroprevalence with age was seen for all racial/ethnic groups.

Statewide, minority women (black or Hispanic) seen in family planning clinics had an HIV seroprevalence rate of 0.76%, or six times the rate seen in non-Hispanic white clients. An overall increasing or decreasing trend in the prevalence of HIV infection among family planning clients was not detected during the study period.

Runaway and Homeless Adolescents

This study window was designed to determine the HIV seroprevalence of adolescents receiving health care at Covenant House, to ascertain selected epidemiologic characteristics (age, race, ethnicity, sex, county of last residence), to detect changes in seroprevalence over time and determine risk factors associated with HIV infection in this population. Although this population is not representative of adolescents in general, the facility was selected to serve as a sentinel to determine trends of infection in high-risk youth.

Over the 27-month study period, 2,667 specimens were analyzed for HIV antibody, and 142 (5.3%) were found to be HIV seropositive. The highest rate, 7.9%, was detected in the fourth quarter of 1987, and the lowest rate, 2.5%, was seen in the fourth quarter of 1989. There was a tendency toward a decrease in seroprevalence over time, but the decline was not significant. The seroprevalence rate was 4.2% for females (42/1,037) and 6.0% for males (97/1,611). This difference was not statistically significant. The seroprevalence rate increased with increasing age from 1.3% for 15-year olds to 8.6% for 20-year olds. Of those individuals with an identified racial/ethnic status, Hispanics had the highest seroprevalence rate (6.8%) followed by non-hispanic whites (6.0%) and non-hispanic blacks (4.6%).

The AIDS Epidemic

The number of AIDS cases diagnosed statewide has increased every year through 1988. It is the leading cause of death among men 30–49-years old and women 20–39-

years old in New York City, as well as among 30–39 year old minorities in the rest of the state. New York City reported 22,231 (84%) of statewide cases through November 1989.

The epidemiology of AIDS has been easily influenced by the large number of cases among intravenous drug users. Whereas IVDU accounts for 16% of adult/adolescent AIDS cases in the rest of the nation, it accounts for 39% of the cases in New York State. IVDU is the leading exposure category among racial minorities, with a disproportionately high rate of cases among blacks and Hispanics. The epidemic among women and children has also been severe, resulting from IVDU by women, heterosexual transmission from drug users to women and perinatal transmission to their children.

Summary

Seroprevalence determinations of HIV are essential for design and implementation of preventive strategies. By demonstrating the severity of HIV infections within communities, New York State surveys have spurred preventive interventions, including information to the public and healthcare providers and increased counseling and testing of women of reproductive age. Community health workers have been employed in preventive activities in high prevalence areas. Information has been provided to county health departments on zip code areas with high HIV seroprevalence rates. Serosurveys revealed that the magnitude of HIV infection in adolescents is much larger than indicated by case reports. Various seroprevalence studies confirmed higher rates of infection with increasing age and minority status and a strong association with intravenous drug use. Combining data provided by seroprevalence studies in a given community enables planners to assess the extent of infection in that community and in groups important to transmission of the virus.

Disability prevention program

The New York State Department of Health's Disability Prevention Program is developing a state strategic plan that calls for statewide and community projects, legislation, and public education to reduce the incidence and/or severity of injury-related, developmental and secondary disabilities.

This program has funded a number of community projects over the past three years. Two such projects, one conducted by the Health Science Center of the State University of New York at Syracuse and the other by the New York State Office of Mental Retardation and Developmental Disabilities (OMRDD), focus on the improved surveillance of disabilities.

Working in conjunction with local school districts, the Health Science Center is collecting data on injuries in school-aged children, including information on the causes, circumstances and severity of injuries, as well as medical care provided and the outcomes. The project's goal is to develop a comprehensive data base for head

and spinal cord injuries in school-aged children that will assist in the development of school-based interventions to prevent these serious and often disabling impairments.

The OMRDD project identifies secondary conditions in people with cerebral palsy who are part of OMRDD's client tracking system, the "Development Disabilities Profile," which collects information on clients' residences, health characteristics, and behaviors.

In addition to these two projects, the Disability Prevention Program awarded smaller grants, totaling \$55,200, to seven local health departments. These grants support community projects designed to decrease the incidence of disabilities due to the following: head and spinal cord injuries, burns, lead poisoning, drug and alcohol use during pregnancy, and hearing and visual impairments. The community-based programs include child safety seat loan programs, education regarding drug and alcohol use during pregnancy, and workshops for physicians and nurses on the dangers of lead poisoning.

For more information on the Disability Prevention Program, contact Fran Stevens, Manager, Disability Prevention Program, at the New York State Department of Health Disability Prevention Program, Empire State Plaza, Room 621, Corning Tower, Albany, NY 12237-0608.

Childhood burn injury video

Fires and burns are the leading cause of home injury deaths among children under 15 in New York State. Hot liquid burns are the leading cause of nonfatal burns for this age group and result from hot beverages, foods, and tap water. Other nonfatal burns that most frequently occur in and around the home are due to cooking, structure fires, or contact with hot objects or fireworks.

To help address the problem of burn injury in the home, the New York State Department of Health's Injury Control Program produced the video, "How to Prevent Childhood Burn Injury." The format of this 35 minute video is similar to the popular television show "This Old House," taking the viewer on a tour of a typical house in a relaxed and informal manner to identify risk factors in the home related to burn injury.

The video will be distributed to all local health units along with burn injury prevention packets prepared by the Injury Control Program. For more information on the use and/or availability of the "How to Prevent Childhood Burn Injury" video, contact the Injury Control Program, NYS Department of Health, Corning Tower, Room 621 Albany, NY 12237

The production of this video was supported in part by project #MCJ-363002 from the Maternal and Child Health Program, Health Resources and Services Administration, US Department of Health and Human Services.

Additional medications and expansion of medical criteria through the AIDS drug assistance program

The AIDS Drug Assistance Program (ADAP) recently expanded its drug formulary to include 11 additional medications for the treatment of HIV infection or AIDS. In addition, the medical criteria have been broadened to allow for earlier treatment in the prevention of *Pneumocystis carinii* pneumonia (PCP). These changes went into effect July 1, 1991. ADAP is a federally funded program providing US Food and Drug Administration (FDA) approved drugs without cost to New York State residents seeking treatment for HIV infection or AIDS and who have inadequate or no insurance coverage, are not eligible for Medicaid, and meet medical eligibility criteria.

The ADAP program began in September 1987 to help ensure access to AZT for all New Yorkers infected with HIV. In June 1989, the scope of the program was expanded to cover other FDA-approved drugs found effective in prolonging life through treatment or prevention of HIV-related illness. These included α -interferon (indicated for treatment of Kaposi's sarcoma), along with three additional drugs (aerosolized pentamidine, trimethoprim-sulfa-methoxazole for PCP prophylaxis.

The new medications include the following:

- Amphotericin B for treatment of cryptococcal meningitis
- Pyrimethamine, sulfadiazine, triple sulfa, clindamycin, and leucovorin for treatment of toxoplasmosis
- Doxorubicin, bleomycin, etoposide, vinblastine, and vincristine for treatment of Kaposi's sarcoma.

The change in medical criteria will allow individuals with a diagnosis of AIDS or a CD4⁺ count less than 300/mm³ to begin early treatment for the prevention of PCP. Originally, the criteria allowed only those individuals with a history of PCP or a CD4⁺ count less than 200/mm³ to receive early treatment for PCP. This change in the criteria will allow more individuals to be eligible for PCP prophylaxis.

The ADAP formulary now consists of 25 medications for the treatment of HIV and various opportunistic infections. These medications are provided through federal funds allocated to New York State and New York City. Over 9,200 individuals have enrolled in ADAP since October 1987 and more than 5,300 individuals are currently active participants.

Individuals who wish to apply or find out more about the ADAP program may call the toll-free hotline at 1-800-542-2437.

A review of food-borne disease outbreaks in New York State—1989

Since 1980 the New York State Department of Health (NYSDOH), supported by local health departments,

has maintained a food-borne disease surveillance program. The program uses a team approach involving public health physicians, nurses, sanitarians, administrators, epidemiologists, and health inspectors. Food-borne disease surveillance is valuable for several reasons: for disease prevention and control, to provide increased knowledge of disease causation, and for administrative guidance. A review of food-borne disease outbreaks in New York State is published annually.

From 1980 through 1989, a total of 1,261 outbreaks involving 26,183 cases of illnesses and 23 deaths were reported. In 1989, 150 outbreaks of food-borne disease involving 1,979 cases, four deaths and 147 hospitalizations were reported.

From 1980 through 1989, 178 outbreaks and 4,469 cases of food-borne illnesses with a salmonella etiology were reported. In 1989, salmonellosis was the single most often reported food-borne disease etiology for the eighth consecutive year. Of the 57, 37 (65%) confirmed bacterial outbreaks were associated with salmonella; 24 of these were further identified as serogroup D. Of the latter group, 21 were serotyped as salmonella serotype enteritidis.

During this same time period, 322 outbreaks and 8,979 cases of illness of both confirmed or suspected viral etiology were reported. The greatest number of viral outbreaks since 1982 (113) were reported in 1989 (41). The increased number of viral etiology outbreaks reported in 1982 were associated with the consumption of raw or lightly cooked clams or oysters (110 outbreaks). Consumption of raw or lightly cooked clams was also responsible for the increased number of viral etiology outbreaks in 1989 (11 outbreaks). For the time period 1980 through 1989, Norwalk agent was the most frequently identified viral etiology (23 outbreaks), followed by hepatitis A (14 outbreaks) and rotavirus (11 outbreaks).

Vehicles of Transmission

Eggs were the most frequently reported vehicle of food-borne illness in 1989 with 14 outbreaks involving 188 cases of illness; salmonella serotype enteritidis was identified in 11 of these outbreaks involving 155 cases of illness. Poultry and shellfish (raw hard shell clams) were reported as vehicles of food-borne illness in 11 outbreaks each and accounted for 131 and 148 cases of illness respectively. Salads (potato, fruit, chef, macaroni, seafood, and pasta salads) were reported as vehicles of food-borne illness in ten outbreaks and accounted for the most cases of food-borne illness of any vehicle reported (442 cases of illness). Other vehicles of food-borne illness reported in 1989 included multiple foods, fin fish, and Chinese foods in eight outbreaks each; beef in seven outbreaks; seafood in six outbreaks; beverages in five outbreaks (orange juice served at an upstate New York resort was implicated in a typhoid fever outbreak); and mushrooms (canned in the People's Republic of China and contaminated with staphylococcal enterotoxin) and Mexican food in four outbreaks each. Green salads, Italian food and other vehicles (commercially canned garlic in extra virgin olive oil was linked to three

cases of type A botulism) were also implicated in two outbreaks each.

Place Where Food Was Mishandled

The place where the food associated with an outbreak was mishandled in some manner was identified in 93 of the 150 outbreaks occurring in 1989. The actual food source; that is, the site of production and/or harvest of raw foods, specifically the farms where shell eggs were produced or the water where shellfish were harvested, was implicated in 23 of the 93 outbreaks (24.7%).

Contributing Factors

One or more contributing factors were identified in 85 of 150 outbreaks (56.7%). Of the confirmed outbreaks, 55 of 70 (78.6%) had contributing factors reported, compared with 30 of 80 (37.5%) of the suspected and unknown etiologies.

Improper cooling/refrigeration was reported in 37 of 85 (43.5%) outbreaks for which contributing factors were reported and, as in 1988, was the most frequently reported factor. In 1989, inadequate cooking was reported in 29 of 85 (34.1%) outbreaks for which contributing factors were reported and was the second most frequently reported factor. In 1988, inadequate cooking was reported in 15 of 69 (21.7%) outbreaks. The increased number reported in 1989 was due to the increase in the number of shellfish-associated viral gastroenteritis and shell-egg-associated salmonellosis outbreaks reported in 1989 compared with 1988. Contaminated ingredients were reported in 21 of 85 (24.7%) outbreaks for which contributing factors were reported and was the third most frequently reported contributing factor. Contaminated ingredients were a contributing factor in shell egg-associated salmonellosis and staphylococcal intoxications from canned mushrooms. The infected person category was reported to contribute to 12 of 85 (14.7%) outbreaks for which contributing factors were reported and was the fourth most frequently reported factor. In 1988, the infected person category was the second most frequently reported contributing factor.

Control Measures

In 1985, the Bureau of Community Sanitation and Food Protection advised local health departments to focus the emphasis during facility inspections on identifying practices associated with food-borne illness (for example, improper cooling/refrigeration, inadequate cooking, food service workers who handle foods while ill with a disease capable of being transmitted by food) and on eliminating these practices. Components of this approach, known as Hazard Analysis Critical Control Points (HACCP), include the following:

1. A hazard analysis to identify operations in which foods could become contaminated,
2. Identification of critical control points,
3. Establishing criteria and implementing control measures,
4. Monitoring of operations at each critical control point,

5. Taking action whenever monitoring results indicate criteria are not met,
6. Verifying effectiveness of the HACCP plan and monitoring.

This approach has been reinforced through standardized training of inspectors which allows for uniformity in identifying practices associated with food-borne illness and emphasis on enforcement to eliminate such practices.

New Yorkers consume more than three billion meals a year at 60,000 schools, senior citizen centers, institutions, food service establishments, hotels and motels, and fairs. Inspections in 150,000 of these regulated sites, along with 150 outbreak investigations, were conducted by the New York State Department of Health environmental health staff in 1989.

Whenever sources of contaminated foods are identified (for example, shell eggs, raw hard-shelled clams, canned mushrooms), cooperative actions such as embargoes and testing of sources are initiated in conjunction with other state (Departments of Environmental Conservation and Agriculture and Markets) and federal (Food and Drug Administration, Department of Agriculture) agencies to prevent the sale and distribution of contaminated foods to the consumer.

Reporting of suspected food-borne illness is essential to identify contaminated sources of food practices leading to food-borne illness and to prevent further food-borne illnesses. Anyone who becomes aware of incidents of suspected food-borne illness should report them immediately to their local health department. Additional information on food-borne illness in New York State can be obtained by contacting the New York State Department of Health, Bureau of Community Sanitation and Food Protection, II University Place, Albany, NY 12203-3313. (518) 458-6706.

ERRATUM

In the August 1991 Leads From Epidemiology Notes, an article appeared providing an update on *Haemophilus influenzae* type B (HIB) vaccination. Table III of the article outlined the recommended HIB vaccination schedule for children older than two months of age at the time of the first dose of HIB vaccine. For the PRP-OMP (Merck, Sharp, and Dohne) vaccine, a booster at 15 months of age is recommended for those children receiving their first dose between the ages of 12-14 months. This information was not originally included in the table.

DIAGNOSIS AND TREATMENT OF EXTRAUTERINE PREGNANCIES

Edited by Nicholas Kadar, MD, 256 pp, illustrated. New York, Raven Press, 1990. \$78.00 (hardcover)

This is an extraordinary book. In his foreward, Dr James H. Nelson considers the question of the need for a text on ectopic pregnancy. His conclusion is that a strong need exists. Ectopic pregnancy is the most common cause of maternal death among non-Caucasian women in the United States, and regardless of race, it is the most common cause of death in the first 20 weeks of pregnancy. Two-thirds of the deaths are still considered preventable. Dr Kadar's objectives are to bring together the massive data which have accumulated on the subject of extrauterine pregnancies over the last decade and to subject those data to critical and objective analysis. The author is uniquely qualified to address this topic, having published extensively on the subject, and being personally involved in research on the discriminatory zone levels of human chorionic gonadotropin.

The book is organized into five divisions. The first provides the background material on patho-physiology, epidemiology, and etiology. The second focuses on the diagnosis of tubal pregnancy, and the third on the treatment of tubal pregnancy. The fourth division discusses the diagnosis and treatment and nontubal ectopic pregnancy. The fifth division is itself divided into five appendices, the first of which discusses regression analysis. The second appendix addresses the biology of hCG, hCG standards, and hCG assays, and the third provides methods of assessing the diagnostic value of medical tests. The fourth appendix presents material on exponential functions and distribution while the final part discusses miscellaneous statistical methods. The organization as described would scarcely prepare the prospective reader for the enormous and exhaustive discussion provided in the chapters within each division. Two of the chapters in the first division, those devoted to the characteristics of extrauterine implantation and pathology of tubal pregnancy, are excellent.

In the second division, the critical analysis of the role ultrasound and hCG tests play in the diagnosis is extraordinary. It is here the author displays a singular talent for objectivity.

The varieties of operative techniques, both ablative and conservative, are presented and followed by a most complete discussion of the advantages of each. The current interest in the non-operative treatment of tubal pregnancies is addressed in depth.

There are six chapters on nontubal ectopic pregnancy, with complete material on ovarian, cervical, abdominal, and heterotopic pregnancies. The bibliographies with each chapter attest to the enormous time and research the author devoted to his work. The inclusion of the appendices to assist those interested in the statistical analysis contribute to the completeness of this excellent book.

Dr Kadar has made significant contributions in the past to our understanding of extrauterine pregnancy, but with the publication of this beautifully written book, he has clearly achieved his objectives. It should be read by everyone who may be involved in the health care of women.

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IRRITABLE BOWEL SYNDROME: ONE DISEASE, SEVERAL, OR NONE?

Volume 5. Edited by G. Bianchi Porro and N.W. Read. 82 pp, illustrated. New York, Raven Press, 1990. \$38.00 (hardcover)

This book represents a compendium of lectures delivered during the morning session of the 10th Congress of the Association for Gastroenterology and Endoscopy held in Sirmione, Italy, in May 1988. It is the fifth of six books in a series entitled *Perspectives in Digestive Disease* by the same editor. Its stated purpose is to generate interest in and a desire to study the problem of the irritable bowel syndrome, a common problem encountered by many physicians in their

day-to-day clinical practice. It achieves this goal admirably.

It is my belief that most practicing physicians learn about irritable bowel syndrome primarily from listening to their patients who suffer from the disorder(s). Diagnostic evaluation is aimed at excluding more serious forms of digestive diseases and often includes routing laboratory blood work as well as radiographic and endoscopic examination in addition to microbiologic testing of the stool for parasites (particularly if there is a travel history). Time is devoted to learning about those factors in a patient's past medical, family, and social histories that may be at play. Research to date, often focused on intestinal motility and transit, has failed to provide the precise pathogenesis of the disorder(s) nor has it provided universally effective pharmacologic agents for treatment. As current treatment is often unsatisfactory, particularly severe or refractory cases often result in frustration on the part of the physician and patient.

The 12 contributors to this book are all Europeans, there being no representation from the United States, Canada, or Japan. Its nine chapters are easily readable, balanced and well-written. Covering a workable definition of irritable bowel syndrome, its history, pathophysiology, diagnosis, and currently available treatment, including psychotherapy and diet therapy, the reader will come away from this book with a well-rounded overview of irritable bowel syndrome as it is currently incompletely understood.

Although I would take issue with the terms "neurotic bowel" and "demented bowel" as subclassifications of the irritable bowel syndrome in the chapter on new concepts and therapeutic implications, I would highly recommend the chapters on definition and pathophysiology (a nice, balanced review of recent reports in the field) and the chapter on psychiatric disturbances in irritable bowel syndrome. For those who prescribe bran for their patients with irritable bowel syndrome, a chapter dealing with this practice will make interesting reading.

At a price of \$38.00, this hardcover book of 82 pages may be prohibitively expensive to a large medical audience in the United States. Nevertheless, it

belongs in major medical libraries as a single up-to-date source of information about this common condition and our incomplete understanding of it. It should be required reading for gastroenterology fellows (whose hospital-based training rarely permits much exposure to this clinical entity) and will be of interest to practicing gastroenterologists and internists in general. If this book is representative of the other volumes in the series edited by Dr Porro, they, too should make interesting reading for those with an interest in gastroenterology.

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**PROGRESS IN ENDOCRINE RESEARCH
AND THERAPY. VOLUME 5. ACTH,
CUSHING'S SYNDROME AND OTHER
HYPERCORTISOLEMIC STATES**

Edited by Dieter K. Ludecke, MD,
George P. Chrousos, MD, and George
Tolis, MD. 336 pp, illustrated. New
York, Raven Press, 1990. \$95.00 (hard-
cover)

This book is the fifth in a series entitled *Progress in Endocrine Research and Therapy* published since 1984. It is a compilation of 41 papers presented at a symposium on ACTH hypersecretion sponsored by the European Neuroendocrine Association in April 1989 in Greece. The contributors, representing 13 countries, are all recognized authorities in the areas of hypercortisolemic states. The individual papers have been grouped into ten areas including the basic physiology of the pituitary-adrenal axis, a review of the peptides involved in ACTH secretion, the various forms of Cushing's syndrome, differences in the clinical evaluation of Cushing's syndrome, pituitary and adrenal pathology, and the different modes of medical and surgical therapy. One group entitled "Specific Issues of Hypercortisolism" is a particularly nice collection of papers which discusses specific issues on hypercortisolism such as glucocorticoid therapy, the role of the glucocorticoids in the immune system, paracrine effects of CRH, glucocorticoids and bone physiology, and influences on

blood pressure and gonadal function. Many of the topics were reviewed from a pathophysiologic viewpoint and at the time contained a variety of unpublished data.

The book is an interesting compilation of many individuals' significant contributions to this field. Its appeal will be primarily to those interested in the field of neuroendocrinology and to those who deal with hypercortisolemic states (predominantly endocrinologists). The detail concerning these states is greater in this volume than in standard textbooks. Therefore, it may not have significant value to internists, pediatricians, or others not dealing with these problems on a regular basis. The individual manuscripts were obviously submitted and photo-reproduced. Because of that, there is some variation in quality, type styles, and graphic or photo-reproduction among them. Additionally, these manuscripts were obviously not fully edited and in some instances suffer because of the imprecise English translations by the authors.

There are several series of monographs derived from national and international meetings in specific areas in endocrinology. This book does not have any particular merit compared with others of this class, but does serve as a reasonably up-to-date compilation of a wide variety of topics related to hypercortisolemic states. For those involved in research in this area, this book should stimulate some thought concerning the resolution of some problems that exist in the management of hypercortisolemic states.

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**HALLUCINATIONS IN CLINICAL
PSYCHIATRY: A GUIDE FOR MENTAL
HEALTH PROFESSIONALS**

By Ghazi Asaad, MD. 160 pp, New
York, Brunner/Mazel Publishers,
1990. \$21.95 (hardcover)

This volume focuses on the diagnosis, treatment, and other clinical issues relevant to the hallucinatory phenomenon. As the author states, the purpose of this book, is to offer a practical guide to the clinician in the assessment of hallucinatory symptoms as they present in various conditions, psychiatric and otherwise.

The book is divided into 18 brief but very well thought out chapters and it includes a thorough bibliography. The author, who is the director of inpatient psychiatric services at Danbury Hospital, begins by going over the history, and the various psychodynamic, psycho-physiological, and neurochemical theories of hallucinations. He follows by summarizing the hallucinatory phenomenon associated with alcoholism, organic mental disorders, and pharmacologic agents. Dr Asaad continues with a discussion of hallucinations and their association with neurologic illness.

There is also a chapter that summarizes hallucinatory episodes in children, and the author's final chapter presents a discussion of an integrative theory of hallucinations.

Dr Asaad has exhaustively and painstakingly looked at the hallucination phenomenon from several different points of view. The chapters are written in a very clear and interesting fashion, and the reference material backs up his careful chapter dialog. This book, which delves into an area of medicine generally not clearly understood, is an important resource for clinicians and students.

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DRUGS IN HISPANIC COMMUNITIES

Edited by Ronald Glick and Joan
Moore. 275 pp. New Brunswick, NJ,
Rutgers University Press, 1990. \$14.00
(softcover) \$37.00 (hardcover)

This book offers a unique contribution to the medical literature because it reviews drug studies that are rarely seen by medical researchers or practitioners. The focus of the book is on Hispanic communities. These studies are reviewed in a readable text, with the organization, unity of theme, and clarity well executed.

The book is divided into four sections. The first looks at the cultural context of Hispanic drug use. The second section offers studies of different Hispanic communities, such as the Cuban community in Miami, Puerto Rican community in New York, the Chicano community in Los Angeles, and others. The third and fourth sections explore treatment and social policies.

The theme of this book centers on Hispanic culture and its unique relationship to the drug experience. Of particular usefulness is the authors' discussion of the various sub-groups within the Hispanic community. The authors point out the importance of geographical location in defining which Hispanic sub-group lives there, ie, Chicano's are more likely to be found in the West and Southwest. The authors then reveal the problems that are unique to each subculture. This identification of unique subcultures affords the practitioner an opportunity to tailor treatment to the patient.

Another point presented is the effect of immigration and assimilation on the dominant culture. It is acknowledged among addiction researchers that as a group assimilates within the dominant culture the rate of addiction increases. This assimilation process is often a source of family difficulties as children enter school and attempt to be accepted. In the process children reject cultural values, causing discord within the family. Another key point made in this book is the important role of the family in the Hispanic culture. This book reveals the relationship between the family and the addict. The pressure on female addicts, for instance, is great.

Another study focuses on the natural course of addiction within a community. In particular, it focuses on Chicago from the 1980s until the present. This is reminiscent of George Vailant's, work which examined the natural history of alcoholism. By so doing, we gain an understanding of the disease process and can better formulate treatment that affects outcome.

This book is strong in the aforementioned points. However, it does have some limitations, especially as a resource for physicians or drug treatment professionals. The authors' qualifications and experiences also limit the perspective. This book may be adequate for social scientists, but it is not state-of-the-art and will appear dated for the average medical practitioner. Medical and biological issues are ignored or only mentioned in passing. Even some modern prevention techniques such as television campaigns, drug testing, evidence of marked drug use differences in high school, and household surveys are ignored. Recent epidemiological data from the National Institute on Drug Abuse show steady decreases in illicit drug

use from 1985, although less than among non-Hispanic whites. Still, in 1990, Hispanic cocaine use was three times that for whites.

We recommend this book to students, practitioners, and those who treat chemically dependent patients for an insight into Hispanic culture as it relates to drug use and addiction.

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HISTORY OF PEDIATRICS, 1850-1950

Volume 22. Edited by Buford L. Nichols, MD, Angel Ballabriga, MD, and Norman Kretchmer, MD. 315 pp, illustrated. New York, Raven Press, 1991. \$56.00 (hardcover)

The eager anticipation I had felt when asked to review *History of Pediatrics, 1850-1950* faded when I first perused the book. Volume 22 in the Nestle's Nutrition Workshop Series, it consists of some 25 addresses each by a different author, delivered at a conference in February, 1989. (The Series constitutes a public relations effort by a corporation that has earned notoriety for its infant formula marketing practices in the developing world). The first several papers, variously titled "French Pediatrics" or "One Century of Pediatrics in Europe" shed singularly little light on the state of the art of medicine in either 1850 or 1950. (Pediatrics was not a separate discipline until late in the epoch). One author, for instance, neglects to translate citations from German, French, and even Swedish. Subsequent chapters describe the history of various pediatric subspecialties. Pediatric gastroenterology gets a chapter although it became a distinct subspecialty after 1950, but infectious disease is a subhead in the chapter "Pediatric Allergy and Immunology" (The era 1850-1950 dawned with the work of Pasteur and culminated with the clinical trials of polio vaccine).

Several of the last chapters, however, gratified my initial expectations. For instance, Calvin Woodruff's chapter "Anemias" begins with the discovery of hemoglobin in 1851, proceeds through the establishment of normal values for the "complete blood count" we now take for granted, and con-

cludes with how the evidence was gathered in the 1950s that underlies our current understanding of iron balance in infancy. The chapter "Salt and Water Disorders" by Jack Metcalf, in which he narrates the first use of intravenous electrolyte solutions to save the lives of cholera victims, is also a masterpiece of medical historical writing. Harold Harrison's account of how the etiology and treatment of rickets was established (which includes evidence gathered at the London Zoo) is a classic story well told.

For a serious exploration of the social and scientific trends that shaped pediatrics, Thomas Cone's *History of American Pediatrics* is a much more satisfying source. However, for a pediatrician with any curiosity about his or her heritage, some of the chapters on selected clinical problems in this volume are worth the effort of winnowing through the chaff.

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THYROID DISEASE: ENDOCRINOLOGY, SURGERY, NUCLEAR MEDICINE, AND RADIOTHERAPY

Edited by Stephen Falk, MD, 670 pp, illustrated. New York, Raven Press, 1990. \$125.00 (hardcover)

Dr Falk and others have endeavored to produce a reference volume on thyroid disease that is unique in that all who come to it, including the endocrinologist, surgeon, anesthesiologist, radiologist, medical student, and others will find a comprehensive, clinically relevant text germane to their particular interest. Indeed, the text is successful and a very useful addition to the library of all physicians who deal with thyroid disorders.

The editor has organized the text to include chapters on physiology, anatomy, embryology, and pathology. Several chapters on thyroid function tests and radiologic imaging are useful preludes to a very thorough discussion of specific thyroid diseases. Treatments of these disorders are logically divided into medical, radiologic, and surgical, each being discussed by an appropriate expert in the field. Overlaps of responsibility and controversy

of management are also clearly discussed. The pathogenesis of various thyroid carcinomas is exceptionally well covered as are the various treatments for carcinoma. The techniques of various surgical procedures are well detailed and illustrated. Complications of therapy are anticipated and thoroughly discussed from all perspectives. Specific chapters on the issue of the solitary thyroid nodule, carcinoma, multinodular goiter, and thyroid needle biopsy will certainly give the novice a "seasoned" approach to sometimes difficult clinical problems. The text tends to be encyclopedic in that practically all issues related to thyroid disease (issues in anesthesia and otolaryngology) are well presented and discussed. The first chapter deals with the history of important milestones in the understanding of thyroid disease and is most fitting in a text of this scope.

Unlike many multi-authored texts this volume reads well. Most chapters represent state of the art within their scope. The chapters are also extensively and appropriately referenced, many citing articles as late as 1988.

As this is the first edition, some minor criticisms seem appropriate. Although the piece on the pathophysiology of Graves' ophthalmopathy is good, the chapters on management of this syndrome should include the issues of radiotherapy and chemotherapy. In addition, a text as comprehensive as this should show similar depth in chapters dealing with calcium metabolism and its disorders. Although the text allows for more than adequate understanding of the complexities of thyroid function studies and the differential diagnosis of hyperthyroidism, the editor should allow some space in future editions for discussing practical approaches (such as decision tree analysis) to these clinical situations. The non-endocrinologist reader will benefit from such additions. The issue of thyroid hormone therapy in patients with ischemic heart disease also needs to be included.

These criticisms aside, this book is excellent in concept, organization, and scope. All who study the thyroid will

find it a very useful resource. It is hoped that future editions will appear with periodic updates.

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**ACADEMIC ENVIRONMENT: A
HANDBOOK FOR EVALUATING
FACULTY EMPLOYMENT
OPPORTUNITIES**

Edited by Karl W. Lanks, MD. 127 pp.
Brooklyn, NY, Faculty Press, Brooklyn, NY, 1990. \$12.95 (softcover)

Anyone who works or plans to work in an academic setting should make a point of reading *The Handbook*. Its purpose is two fold: (1) To provide a practical guide for evaluating present and future jobs in teaching institutions. (2) To present a methodology for objectively assessing the academic atmosphere and working conditions in such institutions.

Each of these two projects comprise a portion of the book. In the first, Dr Lanks offers a concise guide for assessment of job offers. This includes practical pointers for evaluating chairpersons, departments, institutions, and training. *The Handbook* also provides practical suggestions to the dissatisfied academician and details alternative strategies for leaving a job. The author draws on his considerable experience with graduate students and fellows in his position as Professor of Pathology and Director of the Graduate Program in Pathology, at State University of New York Health Science Center at Brooklyn.

In the second part of the book, Dr Lanks presents his research on the assessment of the academic environment. His research employed a questionnaire administered to 836 members of academic medical centers. The results, clearly presented, provide a solid foundation for Dr Lank's stimulating and occasionally counterintuitive conclusions. His most important conclusion is that any organization, as experienced by its members, has an objective reality which is reflected in

(but not reduceable to) measurable indicators. These indicators permit one to compare individual academic centers as Dr Lanks does in tables at the end of the book. Moreover, one can correlate measures of academic atmosphere with objective outcomes such as research, productivity and grant funding.

The book successfully meets both its objectives. The practical guide section represents a useful addition to anyone from recent graduate to departmental chair who must interface with the job market as applicant or employer. This section is written in a lively, concise style with clear "signposts" and summaries that permit easy use.

The research piece adds significantly to our current knowledge about the organizational reality of academic centers. For too long, organizational health has been taken more seriously in the management literature than in medicine. The writing in this section, however, is complicated in its biostatistical explanations and will be less accessible to the general audience. Yet, this work clearly resents the academic environment as an important subject for research by the medical community.

In summary, the book represents an original contribution for those of us who struggle in the job market. I wish it had been available to me long ago. Its major strength is its practicality. This strength paradoxically becomes the book's only significant weakness. Absent from its pages are any suggestions for evaluating the level of research excitement or personal fulfillment. Without an eye on these intangibles, a job search, no matter how intelligently pursued, will be less likely to meet with long term success.

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OBITUARY LISTINGS

Pranas J. Bagdas, MD, Douglaston. Died March 21, 1991; age 79. Dr Bagdas was a 1940 graduate of the Vytauta Didziojo University Medical Fakelteto, Kaunas, Lithuania. He was a member of the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, Inc, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Brijmohan Choudhary, MD, New York. Died June 10, 1991; age 48. Dr Choudhary was a 1965 graduate of Sawai Man Singh Medical College, Rajasthan University, Jaipur, Rajasthan, India. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

George Altman Cohn, MD, Buffalo. Died June 11, 1991; age 71. Dr Cohn was a 1943 graduate of the University of Rochester School of Medicine and Dentistry. He was a Diplomate of the American Board of Neurological Surgery and a Fellow of the American College of Surgeons. His memberships included the American Association of Neurological Surgeons, the Pan American Medical Association, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Biagio DiSalvo, MD, New Rochelle. Died July 11, 1991; age 64. Dr DiSalvo was a 1963 graduate of the Facolta di Medicina e Chirurgia, Universita di Bologna, Bologna, Italy. He was a Fellow of the American College of Angiology. His memberships included the New York State Society of Internal Medicine, the New York Cardiological Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

Thomas R. Downey, MD, St Simons Island, Georgia. Died July 17, 1991; age 61. Dr Downey was a 1958 graduate of Hahnemann University School of Medicine, Philadelphia, Pennsylvania. He was a Diplomate of the American Board of Psychiatry and Neurology and a Fellow of the American Psychiatric Association. He was a member of the Medical Society of the

County of Chemung and the Medical Society of the State of New York.

Mortimer H. Dubovsky, MD, Flushing. Died June 19, 1991; age 77. Dr Dubovsky was a 1941 graduate of the New York University School of Medicine. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Frank Peter Gerold, MD, Pelham. Died September 17, 1990; age 71. Dr Gerold was a 1945 graduate of the New York University School of Medicine. He was a Diplomate of the American Board of Surgery. His memberships included the Society of Surgical Oncology, the American Society of Head and Neck Surgery, the Society of Head and Neck Surgeons, the New York County Medical Society, and the Medical Society of the State of New York.

Armand Arpad-H Grunwald, MD, Jackson Heights. Died July 3, 1991; age 79. Dr Grunwald was a 1940 graduate of the Universite de Pierre et Marie Curie (Paris VI), U.E.R. Brossais-Hotel-Dieu, Paris, France. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Cardiology. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Charles Frank Z. Hawkins, MD, Statesville, North Carolina. Died September 10, 1991; age 95. Dr Hawkins was a 1927 graduate of Cornell University Medical College. He was a member of the Medical Society of the County of Warren and the Medical Society of the State of New York.

Benjamin H. Kaufman, MD, Apopka, Florida. Died July 5, 1991; age 82. Dr Kaufman was a 1935 graduate of the Faculte de Medecine, Universite de Geneve, Geneva, Switzerland. He was a Fellow of the American Academy of Physicians. He was a member of the Medical Society of the County of Chemung and the Medical Society of the State of New York.

Harry Leibowitz, MD, Port Charlotte, Florida. Died July 3, 1991; age 90. Dr

Leibowitz was a 1925 graduate of the State University of New York Health Science Center at Brooklyn, College of Medicine. He was a Fellow of the American College of Allergists. His memberships included the American Academy of Allergy, the American Geriatrics Society, the American Association of Immunologists, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Morton H. Lipsitz, MD, Boca Raton, Florida. Died May 17, 1991; age 78. Dr Lipsitz was a 1938 graduate of the University of Maryland School of Medicine. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. He was a member of the New York Academy of Medicine, the New York State Society of Internal Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Philip Pross, MD, Queens Village. Died July 9, 1991; age 81. Dr Pross was a 1944 graduate of Middlesex University School of Medicine, Waltham, Massachusetts. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

William Bryant Rawls, MD, Pleasant Valley. Died July 17, 1991; age 93. Dr Rawls was a 1922 graduate of Emory University School of Medicine, Atlanta, Georgia. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Gastroenterology and a Fellow of the American College of Physicians. His memberships included the New York Academy of Medicine, the New York State Society of Internal Medicine, the American Rheumatism Association, the American Society of Legal and Industrial Medicine, the American Geriatrics Society, the New York County Medical Society, and the Medical Society of the State of New York.

Benjamin Rosenberg, MD, Boynton Beach, Florida. Died June 20, 1991; age 77. Dr Rosenberg was a 1940 graduate of Virginia Commonwealth University, Medical College of Virginia School of Medicine. He was a

Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Donald Price Ross, MD, Tequesta, Florida. Died August 18, 1990; age 87. Dr Ross was a 1927 graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania. He was a Diplomate of the American Board of Surgery and a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Niagara and the Medical Society of the State of New York.

Richard L. Saunders, MD, Buffalo. Died June 6, 1991; age 89. Dr Saunders was a 1927 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Diplomate of the American Board of Dermatology, Inc. His memberships included the New York State Dermatological Society, the American Academy of Dermatology, the Medical Society of the County of Niagara, and the Medical Society of the State of New York.

Lee Randall Sanborn, MD, Collins. Died May 6, 1991; age 91. Dr Sanborn was a 1924 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. Dr Sanborn was a member of

the New York Academy of Medicine, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Dora Schaffer, MD, New York. Died February 11, 1991; age 78. Dr Schaeffer was a 1937 graduate of the Friedrich-Wilhelms Universitaet Medizinische Fakultaet, Berlin, Germany. She was a Fellow of the American Psychiatric Association. She was a member of the American Psychoanalytic Association, the New York County Medical Society, and the Medical Society of the State of New York.

Marie-Louise Schoelly, MD, New York. Died March 19, 1991; age 76. Dr Schoelly was a 1943 graduate of the Medizinische Fakultaet, Universitaet Zurich, Zurich, Switzerland. She was a member of the American Psychiatric Association, the New York County Medical Society, and the Medical Society of the State of New York.

Vlastimil Straznický, MD, Brooklyn. Died June 11, 1991; age 69. Dr Straznický was a 1955 graduate of the Faculte de Medecine, Universite de Lausanne, Lausanne, Switzerland. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Milton Tarlau, MD, Riegelsville, Pennsylvania. Died June 13, 1991; age 81. Dr Tarlau was a 1934 graduate of the State University of New York Health Science Center at Brooklyn, College

of Medicine. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the New York Neurological Society, the American Academy of Neurology, the American Psychiatric Association, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Max Michael Vinicor, MD, Corinth. Died June 1, 1991; age 77. Dr Vinicor was a 1941 graduate of the Faculte de Medecine, Universite de Lausanne, Lausanne, Switzerland. He was a Fellow of the American Academy of Family Physicians. He was a member of the Medical Society of the County of Saratoga and the Medical Society of the State of New York.

Michael Wolwick, MD, Litchfield, Connecticut. Died June 19, 1991; age 80. Dr Wolwick was a 1938 graduate of the University of Maryland School of Medicine, Baltimore, Maryland. His memberships included the New York Cardiological Society, the American Academy of Family Physicians, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Mike Zouabi, MD, Elmhurst. Died September 10, 1990; age 44. Dr Zouabi was a 1980 graduate of the Universite Catholique de Louvain, Faculte de Medecine, Louvain, Belgium. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

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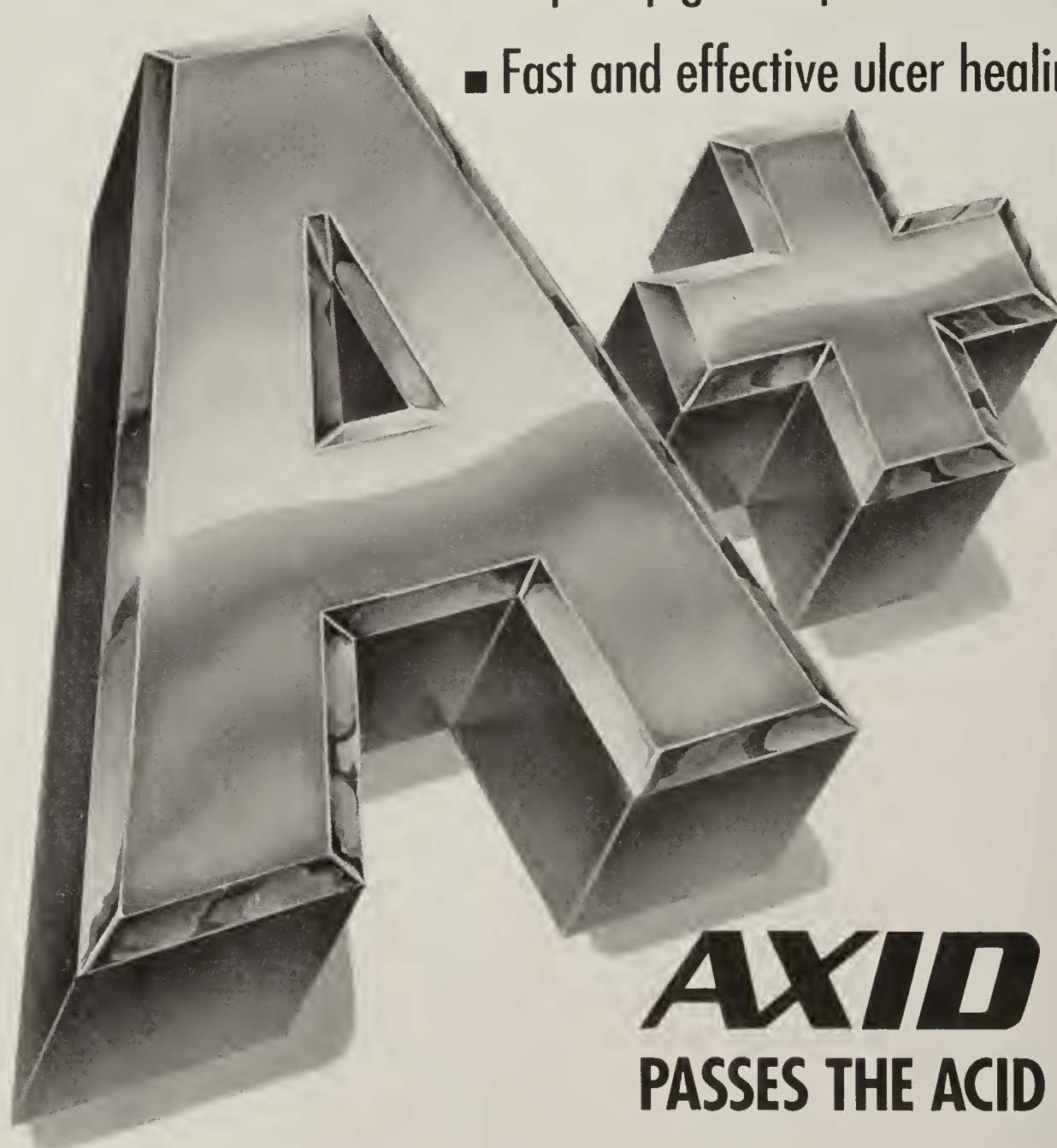
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Drug Interactions—No interactions have been observed with theophylline, chloridazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bilida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H₂-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H₂-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

VP 2091 AMP
[091190]

References

1. Data on file, Lilly Research Laboratories.
2. *Scand J Gastroenterol* 1987;22(suppl 136):61-70.
3. *Scand J Gastroenterol* 1987;22(suppl 136):47-55.
4. *Am J Gastroenterol* 1989;84:769-774.

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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

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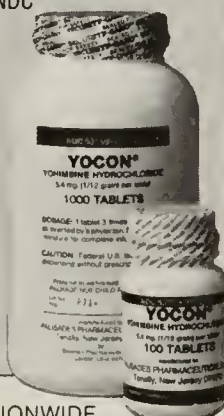
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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Nov 15-16. Endoscopic Issues for the New Decade. Waldorf Astoria Hotel. Contact: NY Society for Gastrointestinal Endoscopy, 40 First Ave, New York, NY 10009. Tel: (212) 777-5176.

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Nov 23. Common Orthopedic Problems in Children. 8 Cat I Credits. Long Island Jewish Medical Center. Contact: Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042. Tel: (718) 470-8650.

RYE BROOK

Nov 6. Headache 1991: A Practical Approach to Diagnosis and Management. 7 Cat I Credits. Rye Town Hilton Hotel. Contact: Mary Bochow, Elkind Headache Center, 20 Archer Ave, Mt Vernon, NY 10550. Tel: (914) 667-2230.

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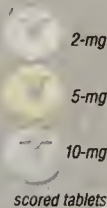
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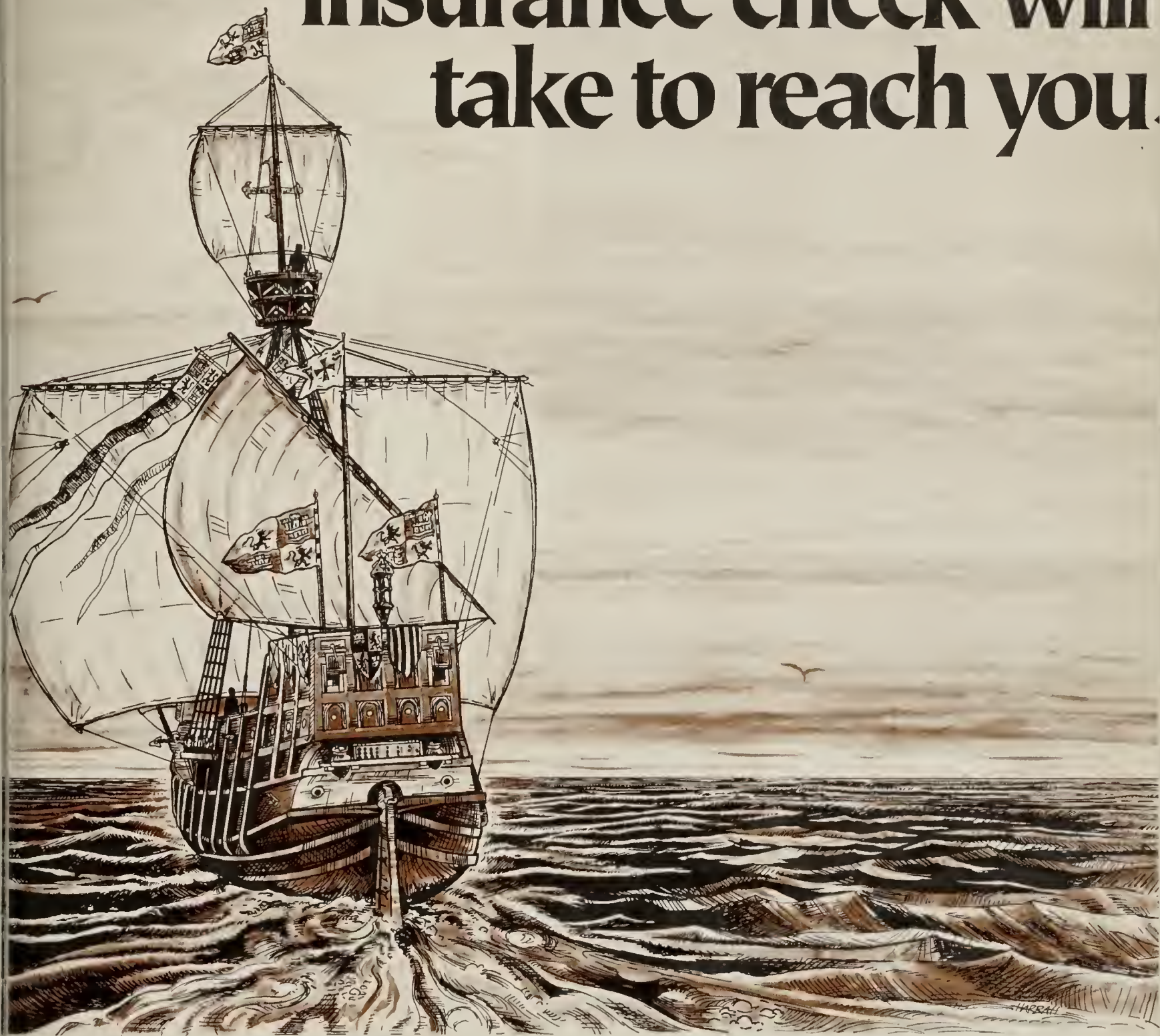
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The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control.

A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature).

Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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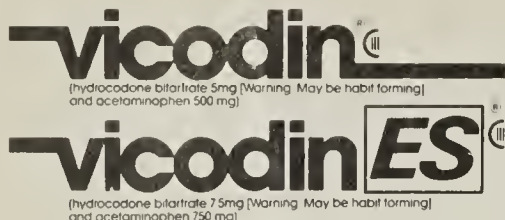
1. Data on file, Knoell Pharmaceuticals

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CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.

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Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS:

Special Risk Patients: VICODIN/VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when VICODIN/VICODIN ES Tablets are used postoperatively and in patients with pulmonary disease.

Drug Interactions: Patients receiving other narcotic analgesics, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with VICODIN/VICODIN ES Tablets may exhibit an additive CNS depression. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy:

Teratogenic Effects: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN/VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever.

Labor and Delivery: Administration of VICODIN/VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN/VICODIN ES Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence and mood changes.

Gastrointestinal System: The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN/VICODIN ES Tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

DRUG ABUSE AND DEPENDENCE:

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Acetaminophen Signs and Symptoms: In acute acetaminophen overdose, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Hydrocodone Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

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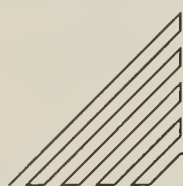
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AROUND THE STATE

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(continued on p 18A)

New York State Journal of Medicine



COMMENTARIES

The vindication of a medical examiner points to the need for reform

In 1985, Elliot M. Gross, MD, the Chief Medical Examiner of New York City, was subjected to allegations in the popular press that he had covered up police brutality by producing misleading and inaccurate autopsy findings. Dr Gross strongly denied these allegations. New York City Mayor, Edward I. Koch, appointed an independent commission to investigate the allegations. This commission was headed by Arthur L. Liman, a Manhattan attorney well known for his years of public service. Several other independent investigations were also launched—by Rudolph W. Giuliani, the United States Attorney for the Southern District of New York, by New York State Attorney General Robert Abrams, by Dr David Axelrod, New York State Commissioner of Health, by Lawrence T. Kurlander, the state's Criminal Justice Coordinator, by Dr David J. Sencer, New York City Commissioner of Health and by Patrick McGinley, New York City Commissioner of Investigation.^{1,2}

In April 1985, the Liman Commission completely exonerated Dr Gross after an exhaustive investigation and after receiving the opinions of leading forensic pathologists from other parts of the country. The commission, however, did conclude that the medical examiner's office was under-staffed, inadequately funded, and under-equipped, at a time when the demand for forensic pathology services was sharply rising.^{3,4} The investigations conducted by Rudolph W. Giuliani and by Charles J. Hynes, the state's special prosecutor for corruption likewise exonerated Dr Gross. The investigations conducted by Drs Axelrod and Sencer and by Commissioner McGinley, found managerial deficiencies in the operations of the Medical Examiner's Office.

In spite of Dr Gross' exoneration by the Liman Commission of allegations that he had engaged in cover-ups of possible police brutality, charges were brought in August, 1985 by then New York State

Commissioner of Health, Dr David Axelrod and the Board for Professional Medical Conduct with regard to autopsies he and his staff had performed and expert testimony he had given in another state as a defense witness. In the fall of 1987, after pressuring Dr Gross to resign, Mayor Koch dismissed him.

The then current hearing procedure for physician discipline in New York State was cumbersome and lengthy and involved six distinct steps. In Dr Gross' case, matters were complicated by legitimate questions raised by his defense attorney as to whether autopsies were medical procedures and whether the board had jurisdiction over them. The Court of Appeals, the state's highest court, finally ruled that the State Board for Professional Medical Conduct could investigate autopsies.

The Board investigated a total of eleven charges of negligence, misconduct, and incompetence involving eight separate autopsies and Dr Gross' trial testimony regarding an autopsy performed in another state. In June 1989, the Board, whose hearing panel consisted of four physicians and a minister-attorney, found no grounds for professional discipline and so informed Dr Axelrod. Although Dr Axelrod received the Board's recommendation in June 1989, he did not issue his own recommendation to the Board of Regents, the final step in the then lengthy review process, until March 1990, nine months later, and then only after Dr Gross had filed a lawsuit against him, charging that the delay had damaged his reputation.

Dr Axelrod recommended to the Regents Review Committee that no disciplinary action be taken. During his review of the charges, he had sought the advice of two medical examiners who used different standards by which to judge Dr Gross' performance. Dr Axelrod stated that it was unfair to find Dr Gross guilty of misconduct in the absence of uniform practice standards. Finally, on July 27, 1990, the New York State Board of Regents dismissed all misconduct charges against Dr Gross.⁶

The opinions expressed are those of the author alone and do not constitute an expression of official opinion of the Medical Society of the State of New York.

Dr Gross' vindication after five years and several lengthy investigations can be but small comfort to a man who diligently served the people of New York City for eight years. During those years, he made repeated requests of the New York City administration to correct the inadequate funding and under-staffing of the Office of the Chief Medical Examiner. City administrators did little to correct these deficiencies which loom large again as New York City struggles through another fiscal crisis.

One outcome of Dr Gross' disciplinary review process was the realization by Dr Axelrod and others that there are many divergent opinions among forensic pathologists about performance standards. In an attempt to deal with this problem, Dr Axelrod appointed a special committee to explore the development of standards by which performance could be objectively assessed. The special article in this issue of the *Journal* by Mitchell et al⁷ explores this subject further and makes recommendations concerning minimum standards for facilities, training, staffing, and performance worthy of very serious consideration. Such reforms, if implemented, would better serve medicine and the public and would repre-

sent a positive outcome of Dr Gross' long and unfair ordeal.

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Neonatal hyperbilirubinemia

The articles in this issue of the *Journal* on neonatal hyperbilirubinemia were originally presented at a conference held at Anaheim, California in May 1990.^{1,2,3} The conference was dedicated to the memory of Leo Stern, MD, (1931-1989), who was Professor and Chairman of the Department of Pediatrics at Brown University and an internationally renowned teacher and investigator in the field of neonatal hyperbilirubinemia. The articles in this issue of the *Journal* explore several current problems and avenues of investigation in the controversy over neonatal hyperbilirubinemia.

It is not controversial that high levels of circulating serum bilirubin can damage the brain, nor is it controversial that the typical asymptomatic case of neonatal hyperbilirubinemia in a term infant seldom does. However, the question whether bilirubin has an independent or contributing effect on later developmental handicap in high risk infants still does not have a clear answer. In addition, there is a trend now to brief hospital stays with early discharge, increased breastfeeding, a changing ethnic and racial composition of the population, and possibly, a less aggressive therapeutic approach to early mild hyperbilirubinemia now than in the past. As a result of the combined effects of these various changes, clinicians now face a new diagnostic and therapeutic problem: what to do with the term infant who develops a serum indirect bilirubin in the low 20s at home? Even in very large follow-up studies, the number of infants seen with untreated bilirubin levels of 20-25 mg/dL or higher is not large enough for accurate prediction of long-term risk. Anecdotal but well-documented cases of acute

bilirubin encephalopathy and long-term handicap are reported for infants with serum indirect bilirubin levels between 24-30 mg/dL. Some of these infants had predisposing factors, such as the Crigler-Najjar Syndrome, but others had no obvious predisposing factors or risk indicators of increased vulnerability.

These cases find their way into the literature from time to time, and perhaps find their way into courtrooms even more often. As a result, the practitioner responsible for the post-discharge care of a newborn infant cannot casually regard bilirubins in the range of 20-25 mg/dL as exceptional variants of normal, but still requiring no further diagnostic studies or treatment. When to treat, how to treat, and when to just watch are questions still lacking precise answers and even an adequate data base in the North American population.

In this issue of the *Journal*, Bratlid reviews some of the experimental evidence for the entry of bilirubin into the nervous system,¹ and Wennberg presents and elaborates on a hypothetical cellular basis for bilirubin toxicity.² In "The hyperbilirubinemic term infant: when to worry, when to treat?" Johnson draws on her vast clinical experience to present selected cases of bilirubin encephalopathy in term infants, with documentation of the acute clinical presentation and long-term follow-up of these patients.³ Some of her patients had obvious additional risk factors, but others did not.

The long-term effects of hyperbilirubinemia in low-birth weight infants also remain unclear. In a follow-up study in the Netherlands several years ago, van de Bor found a positive correlation between serum bilirubin

level and later neurological handicap in small preterm infants closely followed with a high return rate after discharge.⁴ In a sequel to her follow-up work, Dr van de Bor has shown that not all of these associations of hyperbilirubinemia with long-term handicap persist between the second year, when the associations were significant, and the fifth year of age, when some of the associations no longer reached significance.⁵ The confounding variable contributing to both serum bilirubin levels and neurological dysfunction in this population of low-birthweight infants may have been the presence or size of intracranial hemorrhage, causing an early increase in bilirubin production and short-term neurological deficits associated with increased bilirubin but not entirely caused by it, followed by later partial resolution. This is encouraging and leaves open the question how much of the early effect was independently related to serum bilirubin and how much was an indirect relationship mediated through simultaneous effects of intraventricular hemorrhage and increased bilirubin production.

Controversies about bilirubin in the newborn remain unresolved. Even with a less aggressive approach to diagnosis and treatment in the "normal" newborn, practitioners are still left with exceptional cases, as detailed in Lois Johnson's case reports. Such infants may still need to be considered at risk for more than just iatrogenic interference, until we know what the risks are

from severe rather than moderate hyperbilirubinemia in otherwise asymptomatic infants. These infants are appearing in our practices and may need to be followed closely in their immediate post-discharge period. In addition, long-term follow-up of these exceptional cases will be helpful in expanding our knowledge of the spectrum of risk to the central nervous system from bilirubin.

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Observations on neonatal hyperbilirubinemia

In a recent review, *Does Hyperbilirubinemia Damage the Brain of Healthy Full-term Infants?*, Newman and Maisels¹ concluded that for otherwise healthy term babies without hemolysis there was remarkably little evidence of adverse effects of bilirubin on IQ, neurologic examination results, or hearing. Furthermore, they suggested that such infants are probably not at risk for mental or physical impairment until serum bilirubin levels rise well above 20 mg/dL and that aggressive treatment of jaundice in term babies without hemolysis can be questioned. These authors suggested that the stresses associated with a longer hospitalization time, repetitive invasive blood testing, phototherapy routines, and exchange transfusions could pose a health risk to healthy term infants. Furthermore, they indicated that investigation of neonatal jaundice (and the worry that it causes) could have negative consequences on maternal behavior and attitudes in the early, crucial months of infant development. We feel one can question seriously the validity of extrapolating the Newman and Maisels conclusions concerning possible negative aspects of aggressive treatment of jaundice in term babies into reassurance about the general harmlessness of bilirubin in most clinical settings.

That the molecule, bilirubin, can cause cellular and whole organism effects under controlled conditions in the laboratory, and that high levels of bilirubin are

associated with reversible neurologic dysfunction and sometimes irreversible injury, cannot be doubted. That we do not know how bilirubin causes neurologic dysfunction or injury or how to predict which infants will be affected or injured by bilirubin does not translate into the proposition that bilirubin is always harmless below a certain level of bilirubinemia. Moreover, just because a serious event is uncommon or rare in the population (eg, an inherited metabolic disorder like phenylketonuria or congenital hypothyroidism), does not mean that we should not screen for the presence of such disorders and intervene to prevent injury. If there was a consensus about neonatal jaundice, it would likely be that we need to know more about how and when bilirubin can be dangerous to individual newborns, and we need to know what unique vulnerabilities to the pigment exist in premature or sick neonates.

Finally, the interpretation of epidemiologic evidence with the goal being to guide clinical decision-making warrants considerable circumspection, and experimental design always limits clinical relevance. Indeed, it may be appropriate to conclude that, for term newborns without hemolytic disease in the transitional period, neonatal hyperbilirubinemia is not linearly correlated with an increased risk of neurodevelopmental impairment later in life. However, in view of the biochemistry of bilirubin, the experimental evidence for bilirubin

toxicity in cellular and whole animal models and the collective anecdotal experience of clinicians who have observed kernicterus reinforce the concept that there may be a threshold of serum bilirubin above which there is real danger. Furthermore, it is suggested that the threshold may not be the same for all neonates under all conditions. That not all neonates who attain a serum bilirubin level above a particular threshold (eg, 20 mg/dL) are impaired does not obviate this conclusion. Furthermore, it cannot be concluded that all term infants without hemolytic disease and with levels less than the threshold are safe and will not be injured by bilirubin.

In addition, these observations cannot be extrapolated to any other segment of the neonatal population, and some reservations must be assumed with the changing racial and cultural diversity of populations in North America. The same clinical conditions in different racial or cultural settings may represent different relative risks. More research is required to identify which jaundiced babies are at risk and why they are at risk, before any reassurance about the harmlessness of neonatal jaundice can be made and any decision-making on a case-by-case basis can be made truly safe.

As the articles in this issue of the *Journal* by Bratlid,² Wennberg,³ and Johnson⁴ indicate, the final version of

the bilirubin story remains to be told. In the meantime, severe neonatal hyperbilirubinemia should remain a cause for concern in all newborns either as a primary neurotoxic factor, or as a predictor variable for long-term neurologic risk.

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HIV infection among members of the Army Reserve Components residing in New York City

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ABSTRACT. A total of 10,722 members of the US Army Reserve and Army National Guard residing within the five boroughs of New York City (NYC) were tested for antibody to human immunodeficiency virus (HIV). The crude prevalence in NYC was found to be 10.6 per 1,000, compared with a national prevalence of 1.6 per 1,000. The highest prevalences were found among Blacks and Hispanics, males, and among those aged 30–39 years. Patterns of infection were found to be similar to those found among heterosexual and drug abusing populations. Prevalence was highest in the Bronx and varied by less than twofold over all boroughs. Comparisons with reported cases of acquired immunodeficiency syndrome (AIDS) in New York City indicated differences in the demographic and geographic characteristics of the current epidemic of AIDS and HIV infection among members of the Army Reserve components.

(NY State J Med 1991; 91:479–482)

Historically, NYC has been one of the major centers of the AIDS epidemic, with approximately 20% of all reported cases in the United States occurring there.¹ Although the geographic and demographic features of the AIDS epidemic in NYC have been described in detail,² there is less information available regarding HIV infection. Because current AIDS cases reflect HIV infections acquired 5–15 years earlier, information on the distribution and determinants of current HIV infection is required to predict the course of the AIDS epidemic. Unfortunately, the current HIV epidemic are largely invisible, and little is known about the distribution of and factors associated with infection among the general US population. This lack of knowledge makes large-scale, population-based studies of HIV infection all the more valuable in dealing with this epidemic.

Several studies of the prevalence and patterns of HIV infection in NYC have been reported, using estimated numbers of intravenous drug abusers,³ blood samples

collected at health care facilities,⁴ blood samples collected from pregnant women,⁵ cord blood from newborns,⁶ and civilian applicants for military service.⁷ Stoneburner et al⁸ reviewed the incidence of AIDS and HIV infection among heterosexuals in NYC, reporting results from a number of studied groups.

Members of the US Army Reserve (USAR) and Army National Guard (ARNG) provide a large population-based group not selected for testing based on any expected level of risk. Together, the USAR and ARNG comprise the Reserve Components (RC) of the US Army. They represent a population of persons living and working in the civilian sector who are routinely assessed for infection with HIV. Unlike active duty military personnel, members of the RC reside in locations of their own choosing and are under limited military scrutiny and control. They reflect a broad spectrum of adult Americans and provide substantial representation of both sexes, most ethnic groups, and ages from 17 to 62 years.

The purpose of this study was to evaluate the prevalence of HIV infection among RC personnel residing in NYC and to identify demographic and geographic factors associated with infection.

METHODS

It is the policy of the Department of the Army to test all personnel for antibody to HIV at least every two years, including members of the USAR and ANG.⁹ This policy provides a unique opportunity to assess in a serial manner the presence of infection in a well-defined population and to evaluate correlates of the risk of infection. The population under study was defined as those members of the USAR residing in NYC who were registered as active participants at any time between December 1987 and June 1989 and members of the ARNG residing in NYC who participated between July 1986 and July 1988, regardless of when they were tested. Routine testing of the USAR was begun in May 1987 and in June 1986 for the ARNG. Between October 1985 and the dates routine testing began, some personnel were tested before overseas deployment. All testing included in this report occurred between October 1985 and July 1989.

The Army Reserve Personnel Center and the Defense Manpower Data Center routinely provide demographic data for all members of the RC. There is substantial annual turnover in the RC population. Approximately 26% of initial term of service soldiers and 14% of those with six or more years of service ceased

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Portions of this research were presented at the annual meeting of the Society for Epidemiological Research, Snowbird, UT, June 1990.

participation in 1989.¹⁰ Losses are higher among enlisted soldiers than among officers. Individuals leaving the RC are replaced with new enrollees, members resuming participation, and persons leaving active duty military service but continuing their Army affiliation through the RC.

The actual testing of RC personnel is conducted by two laboratories under contract with the Army. All contractors conduct testing according to identical specifications, and the methodology has been described in detail elsewhere.¹¹⁻¹⁴ Blood is drawn from reservists by contract personnel, prepared for shipping on-site, and delivered to a central location for testing. Specimens initially reactive by enzyme-linked immunosorbent assay (ELISA) are retested with ELISA, and if consistently reactive, are confirmed by Western blot analysis. Until May, 1987, specimens were considered positive by Western blot analyses if antibodies were detected either to HIV-encoded proteins gp41 or to p24 and p55. In May 1987, the blot technique was modified, and the definition of positive was changed to evidence of two of the following three: p24, or gp41, or either gp160 or gp120. Specimens are considered positive or negative on the basis of the interpretation in effect at the time of testing. Blots are interpreted by contract personnel, and those who are found positive are further evaluated at the Division of Retrovirology, Walter Reed Army Institute of Research. Attempts are made to retest persons with an initial positive Western blot analysis, usually within two weeks.

Approximately 75% of those individuals positive on initial analysis by Western blot provided a second specimen for confirmation. Those RC personnel who resigned, retired, or transferred to an inactive status failed to have a second specimen drawn, while some had a second specimen pending at the time of data analysis. Personnel were considered infected if an initial and confirmatory Western blot analysis were reactive or if a single Western blot analysis was positive and a confirmatory specimen had not been tested.

Demographic data were merged with the results of HIV antibody tests from the contract testing laboratories, creating one file for analysis. Personal risk behavior information was not available. The latest borough address available was the one used in this report and was determined by the first three digits of the zip code for the home address given.¹⁵

Incidence of infection is not considered in this report. Period prevalence¹⁶ is defined as the number of RC members found positive for HIV infection during the testing period per 1,000 tested. Confidence intervals for univariate measures of prevalence were based on the Poisson distribution. Prevalence ratios¹⁷ for univariate analysis were calculated directly by dividing the prevalence in a comparison group by the prevalence in the reference group, with 95% confidence intervals estimated by Taylor series approximations. To control for confounding between variables, multiple logistic regression was employed to estimate the independent level of risk associated with each demographic factor under consideration,¹⁸ and adjusted odds ratios (AOR) were used as estimates of prevalence ratios. The AOR and confidence interval estimates were calculated on the basis of coefficients and standard errors for each variable under consideration.¹⁹ Variables that were associated with HIV status on univariate analyses were permitted to enter regression models in a stepwise manner.²⁰ If there was evidence that a general main-effects model was not appropriate, the data were stratified and separate models were created for each group under consideration. Specific items of information might have been missing for some individuals, who were then excluded only from the analyses related to those items. For this reason, totals for specific analyses may not add up to the total RC population tested.

RESULTS

Between October 1985 and July 1989, a total of 10,722 members of the RC residing in NYC were tested for the presence of antibody to HIV. Of these, 114 were positive, for a prevalence of 10.6 per 1,000. The prevalence among the 666,711 RC personnel tested who do not live in NYC was 1.4, resulting in a crude

TABLE I. Seroprevalence of HIV Infection by Selected Demographic Factors

Variable	No. Positive	No. Tested	Prevalence 1,000	95% Confidence Interval
Sex				
Female	10	1,802	5.6	2.7-10.2
Male	104	8,917	11.7	9.5-14.1
Ethnicity				
White	9	2,615	3.4	1.6-6.5
Hispanic	30	2,211	13.6	9.2-19.4
Black	72	5,067	14.2	11.8-17.9
Other*	3	735	4.1	0.8-11.9
Age groups (yr)				
≤ 24	16	3,410	4.7	2.7-7.6
25-29	24	2,170	11.1	7.1-16.5
30-34	27	1,450	18.6	12.3-27.1
35-39	23	1,301	17.7	11.2-28.8
40-44	14	1,143	12.2	6.7-20.6
45-49	7	653	10.7	4.3-22.1
≥ 50	3	535	5.6	1.2-16.4
Marital status				
Currently married	45	4,106	11.0	8.0-14.7
Never married	58	4,575	12.7	9.6-16.4

*Includes all other and unknown categories.

prevalence ratio for residence in NYC of 7.5, compared with the rest of the nation.

Table 1 presents the prevalence and 95% Poisson confidence interval estimates for selected demographic factors. Although the prevalences for all demographically defined groups were higher in NYC than for members of the RC nationally,¹¹ the general patterns were similar.

Overall, prevalence was significantly higher among males compared with females, and higher among blacks and Hispanics than whites. However, the limited number of infected females ($n = 10$) and infected whites ($n = 9$) restricted detailed analyses of those groups.

There is some mutual confounding between all factors. To eliminate at least partially the effects of confounding, adjusted odds ratios from multiple logistic regression are presented in Table II, with the reference group for each factor defined as having an odds ratio of 1.0.

The AOR for males was 2.4, which is significantly greater than 1.0. The AOR was also significantly elevated for Hispanics (AOR = 4.1) and blacks (AOR = 4.6). Compared with ratios of those less than 25 years of age, the AORs were significantly higher for all age groups, except those 50 or more years, and highest for those aged 35-39 years (AOR = 4.3). Marital status was a predictor of infection for males but not for females, with those males who were never married having an AOR of 2.1.

As shown in Table III, the prevalence among RC personnel ranged from 7.7 in Queens to 14.4 in the Bronx. However, there were substantial differences in the demographic composition of RC personnel between boroughs. For example, in different boroughs, the proportion of whites ranged from 14% to 88%, and the proportion of blacks ranged from 21% to 57%. When considered in a multiple logistic regression model (adjusting for sex, age, ethnicity, marital status, and occupation), there were no statistically significant differences in prevalence associated with borough of residence.

There were ethnic-specific differences in prevalence within boroughs, as shown in Table IV, but small numbers of infected personnel precluded detailed analysis of intra-borough patterns of infection. In all boroughs, the prevalence among whites was lower than among Hispanics and blacks. In three boroughs, the prevalence was highest among blacks; in two, highest among Hispanics.

TABLE II. Adjusted Prevalence Odds Ratios for HIV Infection by Selected Demographic Factors

Variable	Odds Ratio	95% Confidence Interval
Sex*		
Female	1.0	—
Male	2.4	1.2–4.7
Ethnicity*		
White	1.0	—
Hispanic	4.1	1.9–8.7
Black	4.6	2.3–9.2
Others†	1.2	0.3–4.5
Age groups*		
≤ 24	1.0	—
25–29	2.1	1.1–4.0
30–34	3.9	2.0–7.5
35–39	4.3	2.1–8.6
40–44	2.9	1.3–6.4
45–49	2.7	> 1.0–7.0
≥ 50	1.5	0.4–5.4
Marital status‡		
Currently married	1.0	—
Never married	2.1	1.3–3.2

*Odds ratio based on a model adjusted for sex, ethnicity, age, marital status, and occupation.

†Includes all other and unknown categories.

‡Odds ratio based on a separate model for males only, adjusted for ethnicity, age, marital status, and occupation.

However, none of the black-Hispanic differences were statistically significant.

DISCUSSION

This study of Army Reserve Component personnel living in NYC documents high levels of infection, with a prevalence 7.5 times higher than the rest of the nation. The observed prevalence of over 1% in this population is consistent with other data on HIV seroprevalence in NYC, where the health care system is already struggling with the delivery of services to patients with end stage HIV disease.²¹ Because of the potential non-participation in the Army RC by individuals who are overtly homosexual or are intravenous drug abusers, the observed prevalence is likely an underestimation of the true prevalence of HIV infection among the groups represented in the RC.

Comparisons of patterns of HIV infection among the RC and other studied groups may be useful, but the lack of broad-based seroprevalence studies of HIV makes

TABLE IV. Seroprevalence of HIV Infection by Ethnicity and Borough of Residence

Borough	White	Hispanic	Black
Manhattan	3/449* 6.7†	4/383* 10.4†	13/605* 21.5†
Bronx	2/292 6.8	16/760 21.1	15/1,077 13.9
Brooklyn	2/705 2.8	6/701 8.6	26/1,987 13.1
Queens	1/640 1.6	2/311 6.4	15/1,269 11.8
Staten Island	1/529 1.9	2/54 37.0	3/129 23.3

*Number positive/number tested.

†Prevalence per 1,000.

such comparisons problematic. Because of the potential for substantial selection bias among all study populations, interpretation of comparisons must be done with caution.

The overall patterns of AIDS morbidity and HIV infection in the civilian community are strongly influenced by the impact of male homosexuality, which in NYC is associated with more than 50% of AIDS cases.² It is estimated that the overall prevalence of HIV infection in NYC among males compared with females is approximately eight times higher,²² and that the overall incidence of AIDS is nine times higher among males than females.² However, among presumed heterosexuals, including intravenous drug abusers, the male-to-female ratios of AIDS and HIV infection appear to be substantially lower, by a factor of three to five.^{7,8,22–24} Among RC personnel residing in NYC the adjusted male-to-female ratio was 2.4 (crude prevalence ratio, 2.1).

In NYC there are ethnic specific differences in risk behaviors among AIDS cases,² with male homosexuality being the predominant factor among whites and intravenous drug abuse being relatively more prevalent among blacks and Hispanics. When overall patterns of illness are considered, the ratio of incidence among blacks and Hispanics to that among whites is low. However, when just intravenous drug abusers aged 25–44 were considered, the crude Hispanic-to-white and black-to-white AIDS incidence ratios were about fourfold higher.² There is less ethnic-specific information available for HIV infection.

Among RC members in NYC, the adjusted prevalence among Hispanics was 4.1 times that of whites (crude prevalence ratio, 3.9), and in blacks the adjusted prevalence was 4.6 times that among whites (crude prevalence ratio, 4.1).

These sex- and ethnic-specific patterns of infection observed in the RC population are generally similar to those found in intravenous drug abusers and heterosexual groups, and are dissimilar to the overall incidence of AIDS and prevalence of HIV infection occurring in NYC. The patterns provide evidence that these factors (intravenous drug abuse and heterosexual transmission) may be predominant in maintaining the epidemic among RC personnel in NYC. However, the lack of information on individual risk behaviors for RC personnel precludes a more definitive assessment.

The cumulative incidence of AIDS in Manhattan is more than twice that of the next highest borough, the Bronx, and there is an overall ninefold interborough

TABLE III. Seroprevalence of HIV Infection by Borough of Residence

Borough	No. Positive	No. Tested	Prevalence 1,000	95% Confidence Interval
Manhattan	22	1,562	14.1	8.8–21.3
Bronx	33	2,294	14.4	9.9–20.2
Brooklyn	34	3,627	9.4	6.5–13.1
Queens	19	2,473	7.7	4.6–12.0
Staten Island	6	766	7.8	2.9–17.1

difference in AIDS incidence.² Among RC personnel, the prevalence of HIV is essentially the same in Manhattan and the Bronx, and the prevalences of the highest and lowest boroughs (the Bronx and Staten Island) vary less than twofold. When adjusted for demographic factors known to be associated with infection, borough of residence in itself is not a statistically significant predictor of infection. This lack of variability in infection between boroughs may be predictive of less variability in the rates of clinical HIV disease in the future.

Selection bias can be an important source of error in seroepidemiologic studies and can cause over- or underestimation of infection levels and incorrect identification of groups at increased risk. This can be a particular problem when study participants are not selected by a statistically valid random or probability method, especially when infection is rare.

The magnitude of bias caused by non-participation in the RC by persons who are at particular risk related to behaviors or partner selection practices is unknown. By regulation, persons who engage in homosexual activity or drug abuse are restricted from military service, so there is likely substantial institutional and self deferral of persons who engage in these behaviors. The proportion who practice these behaviors or the frequency of these activities among members of the Reserve Components is unknown. In addition, there may be differential non-participation by different groups at risk of HIV infection (eg, homosexual males as compared to intravenous drug abusers). Because of the relatively infrequent contact with the military (~10% of days per year are spent in training status), persons engaging in risk behaviors may not be detected unless their activities are overt.

The differences between the patterns of infection among RC personnel and those from other surveys may indicate changes in the dynamics and distribution of the infection epidemic as it evolves in NYC. If the patterns of infection among the RC are reflective of the general population, women and minorities may be at relatively greater risk than at earlier stages in the epidemic.

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Hyperbilirubinemia in the term infant: When to worry, when to treat

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The current management of a healthy, jaundiced, term infant and the occurrence of bilirubin-related brain damage in such infants has recently been reassessed.¹⁻⁴ Concern has focused on the use of diagnostic studies and phototherapy in infants with serum bilirubin levels of 20 mg/dL (342 μ mol/L) or less, in the absence of illness or hemolytic disease. This is because the incidence of brain damage in such infants, as evidenced by IQ scores and pure tone audiometry, is very low, even when serum bilirubin levels reach 25-30 mg/dL (428-514 μ mol/L).

Other researchers have related the investigation of jaundice and the use of phototherapy for its treatment to the early termination of breast feeding and development of the vulnerable child syndrome.^{5,6} A "vulnerable child" is defined as the child who is well, but whose parents act as if he or she were not. There are well documented reports of an increased incidence of low motor and mental Bayley scores at the ages of eight months and one year, after controlling for birth weight and gestational age, among hyperbilirubinemic infants enrolled in the Collaborative Study of Cerebral Palsy.^{7,8} However, one author suggests that "the findings of mild behavioral and cognitive delays noted in some infants who were jaundiced as newborns may be due to early effects of the vulnerable child syndrome rather than deposition of bilirubin in the brain."⁵

In considering this possibility, it is important to remember that serum bilirubin levels between 10-20 mg/dL, in the absence of phototherapy or after controlling for its effects, have been shown to have adverse effects on cry characteristics and newborn behavior as assessed by the Brazelton Neonatal Behavioral Assessment Scale.⁹⁻¹¹ The areas principally affected were those involving environmental orientation and behavioral organization, as reflected in decreased scores for inanimate auditory responses and for inanimate and animate visual and auditory responses.^{9,11} These investigators expressed concern about the effect these early behavioral changes might have on the infant-mother interaction. They point out that the most important effect of modest hyperbilirubinemia might be to interfere with the baby's attachment to the mother rather than to compromise future intellectual performance.⁹

Regarding Kemper et al's⁵ suggestion that the current management of jaundice is responsible for the early termination of breast feeding, many possibly confounding factors need to be scrutinized; for example, the 26% incidence of visible bruising among jaundiced as opposed to non-jaundiced infants in her study population. Thus, a mother of an infant with jaundice is apt to be a mother with a sub-optimal milk supply, whose labor and delivery were more difficult, who is tired and upset, whose nipples are flat or inverted, and whose infant is sleepy, uninterested in feeding, less easy to console, loses more weight, and passes stools less frequently. Even in the absence of jaundice, most such mother-infant pairs need added individualized support if they are to establish and continue successful breast feeding.¹²⁻¹⁴ Such mothers might find that the judicious use of formula supplements with or without a breast pump would help, rather than hinder successful breast feeding.

The questions raised by these authors,¹⁻⁶ nevertheless, have validity and need to be addressed. At a minimum, their concerns point to deficiencies in the doctor-patient relationship and to the inability of currently available clinical tests to predict the infant who will develop excessive jaundice and associated brain damage. Both concerns are especially important in the case of infants discharged from the hospital at or before age two days.

EARLY STUDIES OF JAUNDICE IN FULL-TERM INFANTS

In the years before phototherapy, exchange transfusion was recommended for term infants with hemolytic disease at serum bilirubin levels of 20 mg/dL. However, exchange transfusion was not recommended in the case of idiopathic jaundice until levels of 25 mg/dL or greater had been reached. These recommendations were based on a number of small follow-up studies of jaundiced full-term infants with peak serum bilirubin levels of 20 mg/dL or above. Three of these studies were conducted in Scandinavia among infants born between 1956 and 1962.¹⁶⁻¹⁸ The two earlier studies included infants with hemolytic disease and neonatal complications and assessed outcome at age two years.^{16,17} In the first, follow-up included Merrill-Palmer intelligence testing and play audiometry in addition to neurologic and physical examinations.¹⁶ Among the 27 healthy term infants included in this study, no abnormalities were found. In

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the second study,¹⁷ follow-up consisted of a physical and a neurologic examination. No abnormalities were found among the 94 healthy term infants examined, 46 of whom had been treated with exchange transfusion at a bilirubin of 20 mg/dL and 48 of whom had received no treatment. The third study, carried out between 1957 and 1962, was the largest and most rigorous.¹⁸ It considered only healthy term infants born after vaginal delivery in the absence of prolonged labor, difficult delivery, or any other complications and included the healthy full-term infants from Killander et al's earlier study¹⁷ who had not had hemolytic disease. Follow-up, performed between ages 6 and 13 years, consisted of audiologic, neurologic, and psychometric examinations and included a total of 226 infants, 115 of whom had had no visible jaundice, and 111 who had had serum bilirubin levels ≥ 20 mg/dL. The direct Coombs' test was negative in all infants, but in 45 there was blood group system (ABO) incompatibility between infant and mother.

No difference in mean IQ scores was found between jaundiced and non-jaundiced infants. A significant psychologic disturbance (eg, distractibility, short attention span) was found in three of the nonjaundiced and in six of the jaundiced infants, which is a nonsignificant finding.

No cases with hearing loss were identified in children from the nonjaundiced group, but four were found in the jaundiced group without any other identifiable cause on the basis of neonatal, family history, or childhood information. Two of these four hearing-impaired children had been part of the earlier study of Killander et al¹⁷ and had passed as normal on the basis of physical and neurologic examination, without audiometry, at age two years. Their peak serum bilirubin levels, before exchange transfusion, had been 25.6 mg/dL (on day four, with no ABO incompatibility) and 33.2 mg/dL (on day four, with Coombs' negative OA incompatibility). The third child, whose serum bilirubin peaked at 23.7 mg/dL on days seven and ten, had Coombs' negative OA incompatibility, a reticulocytosis of 7.2% and a hemoglobin level of 24 g/dL, and had not been treated with exchange transfusion. In these three children, hearing loss was the only abnormal finding. The fourth child with hearing loss had ABO incompatibility, a reticulocyte count of 1.8% and a peak bilirubin level on day three of 51 mg/dL after an initial exchange transfusion for a bilirubin level of 24.7 mg/dL. This transfusion-related increase in jaundice was unexplained in spite of detailed diagnostic studies and illustrates the risks of this procedure. However, the occurrence of classic kernicterus in such an infant is not germane to this discussion.

In addition to these children with hearing loss, the investigators described a fifth child in whom there was no ABO incompatibility, a reticulocyte count of 8%, and a peak serum bilirubin on day five of 33.2 mg/dL, at which time an exchange transfusion was done. This child had a normal pure tone audiogram. However, at ages three and seven years, the child showed a coordination disturbance of the ataxia-athetosis type, a moderate speech disorder with incorrect word construction and a defective pronunciation, perceptual abnormalities, slight

behavioral problems, (not severe enough to be classified as a psychologic disturbance), and an IQ of 91.

The only child from the nonjaundiced group with abnormal findings at follow-up had a severe behavioral disturbance, a normal audiogram, and an abnormal electroencephalogram. At age 11 years, the child had an IQ of 82 and the additional finding of slight incoordination in the left arm and hand. This child was one of three non-jaundiced children classified as having a psychologic disturbance.

The lack of statistical significance in this data is probably the result of the small number of children with high bilirubin levels and the fact that not all children developed the same type of brain lesion. The investigators concluded that the finding of deficits typical of bilirubin-related brain damage in five of the jaundiced children and in none of the controls, made it highly likely that the deficits were due to hyperbilirubinemia.¹⁸ They concluded that, in full-term infants without isoimmunization, the bilirubin level should not be allowed to exceed 25 mg/dL. In those with possible ABO sensitization, in spite of a negative direct Coombs' test, they made the tentative recommendation that the bilirubin level not be allowed to exceed 20 mg/dL.

These documented instances of bilirubin-related brain damage cannot be lightly dismissed. Although rare, kernicterus does occur in full term healthy infants, and it occurs for no clearly discernible reason in one infant rather than another. There is, in addition, always the possibility that the infant who is healthy and without compromise at hospital discharge may later become not only more jaundiced but also dehydrated, acidotic, or otherwise ill. However difficult it may be, efforts must continue to identify and protect these vulnerable infants.

This position is supported by the large Greek trial of the effect of prenatal phenobarbital on neonatal hyperbilirubinemia.¹⁹ In this trial, a high incidence (9%) of sensorineural hearing loss was found among healthy term infants (some of whom had ABO incompatibility and G6PD deficiency), whose serum bilirubin levels exceeded 12 mg/dL. A 1% incidence of hearing loss was found among infants whose peak serum bilirubin levels had remained below this level ($p < 0.001$, $n = 415$).

The need to identify and protect the vulnerable jaundiced infant is also indicated by the 1979 report of cochlear and brainstem responses in 26 patients with hearing loss cared for in an audiology clinic in Israel.²⁰ Of these 26 patients, 13 had been jaundiced in infancy. Of the 13, 7 had been born at term, had not had hemolytic disease, birth asphyxia, or other perinatal or neonatal complications, and had not had any significant interim illnesses. All had, in addition to moderate-to-severe hearing loss, varying degrees of developmental and motor deficits.

Two of these infants had peak serum indirect bilirubin levels of 16 and 19 mg/dL. The former had been treated with phototherapy; the latter had received no treatment. In two other infants, the peak serum bilirubin levels were 22.5 and 23 mg/dL. The former of these had been treated with exchange transfusion and the latter with phototherapy. Three other infants had bilirubin levels

greater than 25 mg/dL. One, with a bilirubin of 28 mg/dL had been treated with phototherapy and exchange transfusion. One, with a bilirubin of 41 mg/dL had received no treatment, and one, with a bilirubin level of 42.5 mg/dL had been treated with one exchange transfusion.

THE INFLUENCE OF PHOTOTHERAPY

As a result of widespread use of phototherapy, safe, noninvasive control of jaundice is now being accomplished in most infants, and the need for exchange transfusion, on the basis of birth weight and illness designated guidelines, has declined markedly. A temporally related decrease in kernicterus at autopsy in infants requiring intensive care,²¹ and in bilirubin-related morbidity in larger infants,²² has also been seen. It is generally acknowledged that many infants are being treated, using current guidelines, who would not actually have needed treatment. This has been, perhaps, inevitable since we have so limited an ability to predict the infant at higher risk and to define the ideal times and circumstances for instituting phototherapy to obviate the need for exchange transfusion and to facilitate simultaneous discharge of the infant and mother.

Consider the healthy bottle-fed term infant, without ABO incompatibility or G6PD deficiency, whose serum bilirubin at age 42 hours is 13.0 mg/dL. Should phototherapy be started to ensure early hospital discharge? Most of the time probably not. However, we recently saw an infant whose bilirubin at 50 hours was only 13.5 mg/dL. By the morning of the third day (age 66 hours) the level had reached 16.0 mg/dL with an albumin level of 4.5 g/dL. Discharge was delayed until the afternoon, and phototherapy was withheld on the assumption that the bilirubin would fall or plateau in the next few hours. Instead, it rose to 19.8 mg/dL. After 14 hours of 12-bulb superblue phototherapy (and separation from the mother), the bilirubin was still 18.8 mg/dL. (The direct bilirubin was 0.4 mg/dL, 2-(4'-hydroxybenzeneethyl) benzoic acid binding was high (80%), and unbound bilirubin by UB Analyzer was low (0.41 ug/dL.) Subsequently, the bilirubin level fell rapidly. Management of this baby was probably as good as could be expected given usual bilirubin patterns and currently available predictors and treatment modalities. However, sending this baby home on the morning of day three would have been risky, since the bilirubin would probably have risen to the 25 mg/dL range by the next day and phototherapy, delayed until hospital readmission, might not have been adequate to avoid the risk of an exchange transfusion.

What about breastfeeding? When should formula supplements be advised to minimize the need for phototherapy or readmission to the hospital? Consider the completely healthy, full-term, third born, breastfed infant, without blood group incompatibility, who was discharged with a bilirubin level of 10.2 mg/dL on day two for private physician follow-up. The bilirubin on day three was 16.5 mg/dL, and formula supplements were not advised. On day four, the bilirubin was 19.0 mg/dL. Supplements were again not advised, but the infant was sent back to the hospital for evaluation. On admission,

the bilirubin was 21.0 mg/dL. Vigorous phototherapy was instituted and preparations for a possible exchange, which proved unnecessary, were begun. Would formula supplements and institution of a vigorous maximum feeding regime by at least day three have obviated the need for readmission? I think so; at least it would have been worth a try.

THE EXCEPTIONAL INFANT AND EARLY HOSPITAL DISCHARGE

Unfortunately, even conservative management routines for healthy term and near-term infants (36–37 week gestational age) do not protect all vulnerable infants. Recently, a breastfed term infant, without isoimmunization, perinatal illness, or neonatal complications of any sort, was started on phototherapy when the serum bilirubin reached 18 mg/dL. Jaundice in the 18–19 mg/dL range persisted for several days in spite of continuous phototherapy and formula supplements. The bilirubin level fell just as the decision to go ahead with an exchange transfusion was being made. There was no interim illness, toxic exposure, or family history of hearing loss to explain the moderately severe, kernicteric type hearing loss that was found on follow-up examinations (personal communication, D. Bratlid).

This case is disturbing. What put this infant at increased risk? Why was her hyperbilirubinemia so poorly tolerated? Was the albumin unexpectedly low, or for some reason of poor bilirubin binding quality? Did this deficiency of albumin binding, in association with the somewhat prolonged exposure to moderately severe hyperbilirubinemia and, perhaps, an unrecognized minor degree of acidosis, combine to put this infant at greater risk; or, all other things being equal, was the blood brain barrier more immature than usual and the brain less able than usual to clear itself of bilirubin? How can such an infant be identified so that phototherapy can be instituted earlier or more intensively, or exchange transfusion performed at a lower threshold of serum bilirubin?

These questions are especially important for infants discharged before day three in whom neither the bilirubin rise nor minor changes in clinical state can be closely observed. Different hospitals, serving different populations with different ethnic and socioeconomic backgrounds, will need individualized approaches to diagnostic testing routines to facilitate both inpatient and outpatient management. In addition, it will always be important to remember the increased risk associated with the chance coupling of a hemolytic diathesis (eg, hemoglobinopathy, ABO isoimmunization, G6PD deficiency) with infection, even of minor proportions.

Most pediatricians with a large newborn practice have seen examples of "difficult to control" jaundice in healthy term infants during periods of "flu" in the community. Such infants may have viral patterns in single and serial blood counts and, sometimes, stuffy noses. If such infants also have G6PD deficiency or ABO disease, they are at an unpredictably increased risk for excessive hyperbilirubinemia. Discharge on day two should be allowed only if clearly defined and monitored follow-up is prescribed.

Table I provides examples of healthy (six term and one near-term) infants in whom unexpected, severe hyperbilirubinemia developed after hospital discharge. In four, major central nervous system (CNS) deficit consistent with bilirubin brain damage was noted on follow-up. In a fifth, the CNS deficit was not typical of kernicterus. One infant had G6PD deficiency, which was not known at discharge; one had blood group OA sensitization with minimal hemolysis and without an early bilirubin rise. Three infants had no risk factors. At readmission, one of the infants had a staphylococcal diaper rash. One infant, with borderline prematurity

(36–37 weeks gestational age) and subsequent evidence of severe kernicteric brain damage, may have had familial neonatal hyperbilirubinemia, since a subsequent sibling also developed excessive jaundice.

Two additional healthy term infants who developed kernicterus, within the last few years, have recently come to my attention. One was identified as having blood group OB sensitization in the immediate newborn period; in the other, isoimmunization was not diagnosed before hospital discharge. Both infants had a sharp increase in serum bilirubin after discharge and were readmitted too late for exchange transfusion to prevent

TABLE 1. Clinical and Laboratory Findings in Seven Healthy Infants Who Developed Unexpected, Severe Hyperbilirubinemia after Hospital Discharge

Case 1	Normal term pregnancy, labor and delivery; birth weight, 3,742 g. No blood incompatibility. Coombs' negative. Breastfeeding. Phototherapy on days 2 and 3; total serum bilirubin (TSB), 14–15 mg/dL.
Day 4	Discharged; TSB, 14 mg/dL.
Day 11	Peeling, blistering diaper rash. Infant sluggish, irritable, jaundiced. Physician advised of bilirubin level; infant started on antibiotic ointment.
Day 12	Hospital admission. TSB, 27 mg/dL; direct, 1.5; wgt, 3289 g. Irritable, hypertonic, cry high pitched. Treatment, two exchange transfusions, intravenous antibiotics, fluids and phototherapy; G6PD screen and blood cultures negative. Skin grew staph pyodermitis.
Day 14	Cry improved; TSB, 6.5 mg/dL.
Day 20	Discharged. Normal neurologic and physical examination.
Follow-up	Across the board mental deficiency, not suggestive of kernicterus.
Case 2	Normal term pregnancy, labor and delivery. No blood group incompatibility. Coombs' negative. Breastfeeding.
Day 1	Discharged.
Day 4	Hospital admission. TSB, 44 mg/dL; direct, 4.0 units. Normal physical and neurologic examination; hemoglobin, 12.5 g/dL; reticulocyte count, 1.7%, red blood cell electrophoresis and smear normal, G6PD normal, cultures negative. Treatment, two exchange transfusions and phototherapy. BAER* flat.
2 months	Mild unexplained anemia. BAER normal.
6 months	Neurologic and developmental examinations normal.
Case 3	Normal term pregnancy, labor and delivery. Birth weight 3150 g, OA incompatibility, weakly positive Coombs'.
Day 1	Hemoglobin, 14 g/dL; TSB, 6.0 mg/dL; breastfeeding.
Day 2	Discharged. Nursing well.
Day 5	Jaundice noted. Physician visit; TSB, 29.5 mg/dL. Hospital admission. Weight, 3125 g; hemoglobin, 13.9 g/dL; direct, 1.2. BAER abnormal. Treatment: exchange transfusion and phototherapy, 12 hour post-exchange. TSB, 20.6 mg/dL (peak).
Day 7	TSB, 13.0 mg/dL on phototherapy.
Day 9	Discharged. BAER showed prolonged conduction time marked on left, minimal on right.
Follow-up	Age 6 months, results pending.
Case 4	Normal term pregnancy, labor and delivery. No blood incompatibility. Breastfeeding.
Day 1	Discharged.
Day 7	Hospital admission. TSB, 30 mg/dL, cultures negative, G6PD screen negative. Treatment exchange transfusion and phototherapy. BAER flat.
Follow-up	Developmental delay, tight heel cords. BAER flat.
Case 5	Normal term pregnancy, labor and delivery. Birthweight 3785 g. No blood group incompatibility. Breastfeeding.
Day 0	Discharged age 13 hours.
Day 3	Poor feeding, jaundiced. Eyes "rolled up" that night.
Day 4	Hospital admission. TSB, 45 mg/dL. High pitched cry. All cultures and G6PD screen negative. Treatment: exchange transfusion.
Follow-up	Classic signs of kernicterus.
Case 6	Normal pregnancy, labor and delivery. No blood group incompatibility. Breastfeeding. Early hospital discharge.
Day 5	TSB, 12 mg/dL.
Day 6	TSB, 16 mg/dL; direct, 3 mg/dL, total protein, 5.3 g/dL.
Day 7	TSB, 24 mg/dL; direct, 6 mg/dL. Poor feeding. All cultures negative. G6PD screen positive (G6PD deficiency). Pre-exchange TSB, 28 mg/dL; direct, 9 mg/dL. (Exchanged on basis of indirect SB.) Opisthotonic, acute signs of kernicterus.
Follow-up	Classic signs of kernicterus.
Case 7	Normal 36/37 week pregnancy, labor and delivery. Birthweight, 2700 g. No blood group incompatibility. Breastfeeding.
Day 2	Discharged.
Day 8	Hospital admission. Yellow eyes. Decreased crying and feeding. Weight, 2600 g; TSB, 32 mg/dL; direct, 1.0 mg/dL. All cultures and G6PD screen negative; hemoglobin, 15.4 g/dL. Treatment: exchange transfusion, antibiotics, phenobarbital and phototherapy. TSB above 18 mg/dL for next 24 hours. Central apneic spells controlled by theophylline. BAER flat.
Follow-up	Classic signs of kernicterus.

*BAER = brain stem audio evoked response.

brain damage. Protection of these vulnerable infants would have required a higher level of concern and more rigorous and closely monitored follow-up.

MEASURE OF BILIRUBIN-RELATED BRAIN DAMAGE

How should the presence or absence of bilirubin-related brain damage be assessed? Mean IQ is often used as a major criterion^{8,23-27} and so lends itself to meta-analytic statistical techniques. In their overview of the literature, Newman and Maisels³ transformed the mean IQ data, as reported in a number of studies (most importantly in the large Collaborative Project^{23,24}), to a combined mean point IQ decrease per mg/dL increase in peak serum bilirubin, collapsed over socioeconomic groups and race.

Mean IQ is an insensitive measure of bilirubin toxicity.²⁵⁻²⁹ In addition, it is doubtful that the statistical maneuver used is justified from either a theoretical or a practical standpoint. Irreversible, as distinct from reversible, bilirubin compromise of brain function seems to be a threshold phenomenon, with different thresholds for different babies and different conditions. Bilirubin neurotoxicity cannot be reduced to the uniformity implied by a point decrease in IQ per mg/dL increase in serum bilirubin. Some healthy infants are damaged at bilirubin levels that cause no apparent permanent damage to others, and both hearing loss and choreoathetosis can be seen in children with IQ scores well within the normal range.²⁷ Furthermore, there is evidence that minimal brain damage can occur in the absence of motor deficit or high tone hearing loss.^{22, 28-29}

What can be done about the imprecision of serum bilirubin measurements themselves,³⁰ and the general agreement that peak serum bilirubin alone is a poor measure of its toxic potential?^{28,31,32} Consideration must be given to such other factors as the duration of exposure,^{28,32} the associated bilirubin binding reserve,^{28,32} the presence or absence of even minor degrees of acidosis,³³ immaturity or compromise of the blood brain barrier,³⁴ and the potentiation of toxicity by unexpected accomplices such as benzyl alcohol³⁵ or bucolome.³⁶

In spite of all these considerations, it is hard not to be reassured by the statistical overview of Newman and Maisels.³ With reference to the Collaborative Project,²⁴ for example, they report a mere 0.14 IQ point depression for whites and a 0.28 point depression for blacks for each mg/dL increase in bilirubin. That is certainly not impressive although, over a 30 mg/dL serum bilirubin range, this would imply that some children have a 6-point depression of IQ related to hyperbilirubinemia.

A look at the basic data presented in the Collaborative Project reports is revealing.^{23,24} These data, presented as the percent of children with IQ scores below 90 in relation to increasing bilirubin levels, are less reassuring than when transformed into the point for point statistical format.²³ The same is true for the collaborative project results of Broman et al²⁴ showing the mean IQ data for four-year-olds by sex, race, and socioeconomic class as related to low (<10 mg/dL), moderate (10-19 mg/dL), or high (20-28 mg/dL) peak serum bilirubin levels. (Unfortunately, none of the data in these tables were controlled for birth weight or

gestational age). White females of all socioeconomic groups appeared to be at "undetectable" risk, but white males in the middle socioeconomic group showed a 4-point decrease in IQ between high and low bilirubin groups. In the middle socioeconomic groups, black males showed a 5-point decrease, while black females showed a 7.5-point decrease between high and low bilirubin groups.

Considering all socioeconomic groups, there was a 6-point IQ decrease for blacks between high and low bilirubin groups, collapsed over sex. These are mean IQ differences comparable with those associated with "high" or "low" levels of lead exposure.³⁷ Furthermore, high lead exposure was associated with a dearth of superior IQ scores (above 120) and an increase in inferior IQ scores (below 70).

MINIMAL BRAIN DAMAGE

Finally, what about subtle forms of bilirubin-associated brain damage? Do they exist, and, if so, do they matter? Early studies with hearing impaired survivors of Rh disease suggest that they do.^{26,38,39} In addition, our pre-phototherapy study demonstrated that deficits in central hearing, speech, and language can occur in the absence of pure tone hearing loss.^{28,29} We also noted that these deficits are easier to detect at age seven than at age four and that they correlate much more closely with measures of bilirubin binding than with peak serum bilirubin levels.²⁹ These findings are consistent with the following findings of animal and clinical studies⁴⁰: up to 75% of auditory nerve fibers can be destroyed, in animals, without elevation of hearing threshold; humans with acoustic neuromas have poor speech discrimination relative to the pure tone threshold; and small numbers of cochlear nerve fibers can conduct impulses of threshold magnitude, but a greater number is needed to conduct the complex neural patterns of speech.

Our pre-phototherapy study also showed a high incidence of deficit in perceptual functions in spite of normal IQ scores (Fig 1).²⁸ It should be emphasized, however, that this study population had a mean birth weight of $2,772 \pm 732$ g and a mean gestational age of 37.5 ± 3.2 weeks. It included infants with hemolytic disease, illness of varying degrees, and prematurity, as well as completely well term infants. The study is

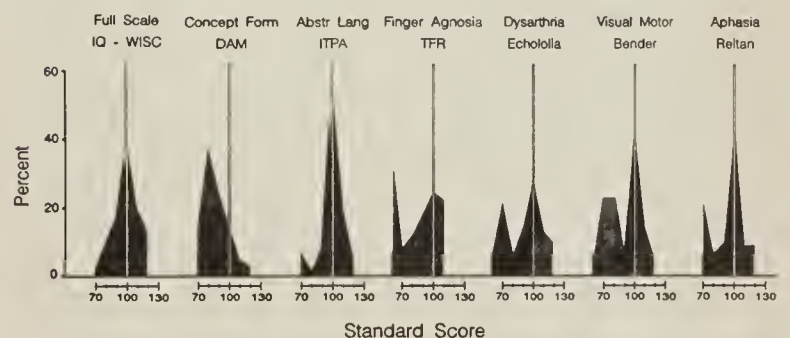


FIGURE 1. Standard scores at age seven years in 64 infants with neonatal jaundice with serum bilirubin levels of 15 mg/dL or higher, born during 1965-1966. Scores of 100 to 109 are grouped at the 100 point; those of 110 to 119 at the 110 point; those of 70 to 79 at the 70 point, etc. The essentially normal distribution of Stanford Binet ratings for IQ and of ITPA ratings for abstract language appear clearly different from the skewed distributions of scores for the five other tests. DAM = draw a man (concept formation), ITPA = abstract language, TFR = tactile finger recognition

mentioned only to emphasize that deficits in central processing can occur in spite of a normal hearing threshold and a normal IQ.

The motor deficits found among jaundiced infants in the Collaborative Project at age one year⁸ after controlling for gestational age and birth weight were not associated with a low mean IQ score or low school achievement at ages four and seven years.^{41,42} This is reassuring but does not negate the existence of the early deficits.

As the Collaborative Project demonstrated, maternal education and socioeconomic factors, over which we, as pediatricians, have little control, are far and away the most important determinants of subsequent IQ and school performance.⁴² These factors, in their magnitude, overshadow perinatal events such as birth asphyxia and neonatal complications such as respiratory distress, apnea, and hyperbilirubinemia.⁴³ This does not mean, however, that perinatal events and neonatal complications are unimportant or deserve more casual management.

CONCLUSIONS

The ideal management of jaundice in the healthy newborn remains an elusive goal. Fortunately, much of the information needed to improve this situation may be available in the near future. Studies are in progress which should allow more effective, less obtrusive forms of phototherapy (eg, Biliblanket Phototherapy Systems), and less invasive, more predictive, and more "user friendly" diagnostic tests.⁴⁴⁻⁵³ New forms of therapy are also being developed to decrease bilirubin production,^{54,55} to augment hepatic bilirubin excretion,^{56,57} and to interrupt the enterohepatic circulation by destroying bilirubin in the gut.⁵⁸

In the meantime, there are simple things that can be done to decrease the risk of over and under treatment of the healthy term newborn. The occurrence of jaundice in association with breastfeeding can be taken as an opportunity for giving the mother individualized counsel and support. Serum albumin can be measured at the time of hospital discharge to assure that at least the average level for a term infant (3.5–3.6 g/dL) is present. If the albumin level is in this range and the infant is healthy, the bilirubin-binding affinity and capacity should also be normal and protective up to at least 20 mg/dL of bilirubin in the serum. Most important, in infants sent home at age two days or less, carefully defined and monitored follow-up should be ordered. The resulting extra contact with health care personnel can then be used as an opportunity to increase the parents' understanding of health and normal development. Last, but not least, we can continue to worry, a little, about all patients, just enough to support the day-to-day disciplines of providing intelligent, concerned, individualized preventive care.

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Bilirubin toxicity: Pathophysiology and assessment of risk factors

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Not long ago kernicterus in the patient with severe erythroblastosis was an ominous development. Today, death caused by classical kernicterus, or otherwise related to hyperbilirubinemia, has become rare in most countries, and the clinical picture of kernicterus has almost been forgotten. The Crigglar-Najjar syndrome with death caused by bilirubin toxicity is also an extremely rare entity, and few physicians are familiar with the homozygous Gunn rat (which also dies from bilirubin toxicity). Thus, the fact that bilirubin is toxic in otherwise normal animals and human newborns does not receive attention.

Although the classical picture of kernicterus is now rarely seen, bilirubin is still found at autopsy in the brains of newborns.¹⁻³ Often the serum bilirubin levels in these infants are only moderately elevated, and the infants have usually been either very premature or small for their gestational age. In other cases, the infants are seriously ill due to various causes in the neonatal period. Symptoms of bilirubin encephalopathy have often been mixed or absent, and it is not clear if these infants die *with* kernicterus or *from* kernicterus.⁴

However, neurologic sequelae other than the classical symptoms, such as retardation of visual perception and disturbances of visual-motor function and non-verbal intellectual function, have been noted in surviving prema-

ture infants who had significant hyperbilirubinemia in the neonatal period.^{5,6} These findings have not only been related to the degree of hyperbilirubinemia, but have also been related to the duration of the jaundice.^{5,6} The very low birthweight, premature infant often has many other complications and problems. Thus, although hyperbilirubinemia is regularly seen in these infants, other complications are usually considered more important as etiologic factors for later developmental deficits.

The purpose of this paper is to review briefly what is known about bilirubin toxicity and the mechanisms by which bilirubin enters the brain.

BILIRUBIN TOXICITY: IN VITRO STUDIES

Several in vitro studies have shown that bilirubin affects and impairs the metabolic functions of various cells and cell systems. The first experimental studies of bilirubin toxicity were published by Day,⁷ who found an inhibitory effect of bilirubin on respiration in brain homogenates. These results were later confirmed by other investigators who concluded that bilirubin was an uncoupler of oxidative phosphorylation in brain mitochondria.⁸ However, this effect is probably not the primary toxic effect in the intact brain.⁹ Several studies have also demonstrated that bilirubin influences the electrical potentials in nerve cells, possibly by its affect on the release of neurotransmitters.¹⁰ Bilirubin has also been found to influence several enzyme systems.¹¹ Fibroblasts incubated with bilirubin/albumin solutions will rapidly die if the molar ratio of bilirubin to albumin in

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the incubate exceeds 1:1.¹² There should therefore be no doubt about the in vitro toxicity of bilirubin.

BILIRUBIN TOXICITY: IN VIVO STUDIES

Toxic effects of bilirubin have also been demonstrated in vivo, for instance in the homozygous Gunn rat. This animal lacks the conjugating enzyme glucuronyltransferase, and as a result has significant hyperbilirubinemia and a high mortality rate in the neonatal period. Bilirubin toxicity has also been demonstrated in other systems. Most of these studies have focused on the neurophysiologic effects of bilirubin in animals, and several of these effects have also been reported in the newborn infant. Particularly well documented are the effects of bilirubin on auditory evoked potentials.¹³⁻¹⁵

Although most of the interest regarding the toxic effects of bilirubin has been focused on the brain, it is obvious that bilirubin also enters other tissues.^{16,17} Its presence in the skin is the basis for the use of phototherapy for treatment of neonatal jaundice. Reduced kidney function has been found both in Gunn rats¹⁸ and in jaundiced newborns.^{19,20}

BILIRUBIN ENTRY INTO THE BRAIN

To exert its toxic effects on the central nervous system, bilirubin has to get into the brain. Short-time carotid perfusion studies in rats seem to indicate that bilirubin might easily penetrate into the brain.^{21,22} Meisel et al^{23,24} measured serum bilirubin concentrations in the cerebrospinal fluid (CSF) and found levels of approximately 5 $\mu\text{mol/L}$ in infants with a mean serum bilirubin concentration of 222 $\mu\text{mol/L}$ (13 mg/dL). This compares well with bilirubin concentrations found in the brain tissue of jaundiced animals.²⁵⁻²⁹

To better understand the complexity of bilirubin toxicity in the newborn infant, several factors have to be evaluated. In addition to the molecular basis for the toxic effects of bilirubin, these factors include the following: how bilirubin enters across the blood-brain barrier; the binding of bilirubin to the neuronal cell and the corresponding symptomatology expressed in the jaundiced infant; and, most important, the relation of these symptoms to the pathologic findings. A schematic simplification of these relations is presented in Figure 1.

Bilirubin probably enters the brain both as the free bilirubin acid salt through an intact blood-brain barrier and as the bilirubin dianion-albumin complex through a disrupted blood-brain barrier. As shown in Figure 1, bilirubin can enter the brain under at least three different conditions,³⁰ as reviewed below.

First, even during physiologic hyperbilirubinemia, there is a steady passage of unbound bilirubin across the blood-brain barrier. This probably colors the brain as well as the cerebrospinal fluid yellow and can be referred to as "brain-icterus." Increases in brain blood flow will increase bilirubin delivery and will increase passage of bilirubin across the blood-brain barrier. Once within the brain tissue, acidosis increases the binding of bilirubin to the nerve cell.

The pathologic significance of this normal brain bilirubin deposition is uncertain. Under normal circumstances, this low level of bilirubin in the brain is probably

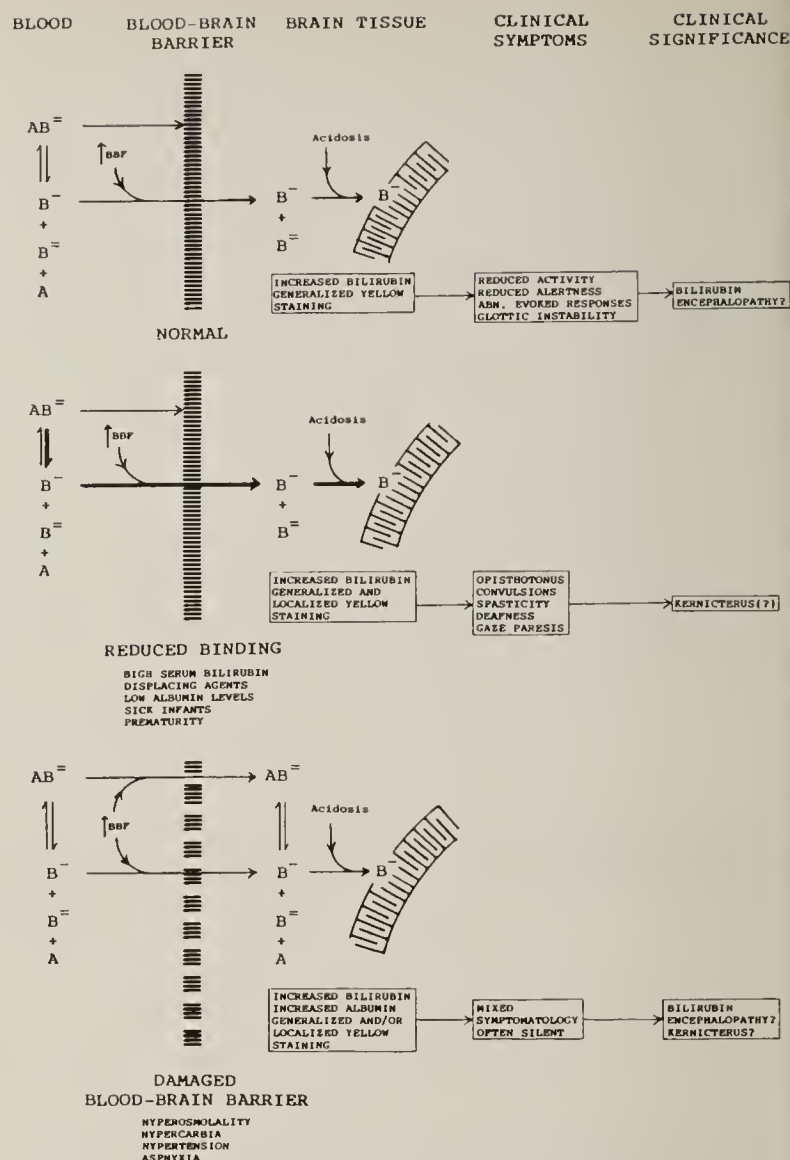


FIGURE 1. Schematic presentation of possible mechanisms for bilirubin entry into the brain and the binding of bilirubin to neuronal cell membranes. The associated clinical symptoms and their possible clinical significance are also shown. The various factors affecting this process are indicated. Abbreviations: A, albumin, AB⁻, albumin-bilirubin complex; B⁻, bilirubin monoanion; B⁼, bilirubin dianion; BDF, brain blood flow. (From Brattlid³⁰)

not harmful. However, significant behavioral and neurophysiologic effects of brain-icterus have been demonstrated in jaundiced newborn infants. Thus, the response to external stimuli, visual orientation, attention, alertness, and motor performance have been found to be lower in jaundiced infants.^{31,32} Likewise, significant effects of this physiologic hyperbilirubinemia have also been demonstrated on auditory brainstem evoked responses (BAER),^{13,14} as well as on visual evoked responses,¹⁴ and cry analysis.¹⁵ It has also been suggested that not only the peak serum bilirubin concentration, but also the duration of hyperbilirubinemia in the infant, correlate with neurodevelopmental outcome.⁶

In patients with very high serum bilirubin levels, this normal entry of bilirubin into the brain can be greatly increased, particularly if the binding capacity of the albumin molecule is exceeded. This increased level of unbound bilirubin within the brain tissue will cause a similarly increased binding to the nerve cells, and the high concentration of unbound bilirubin will finally saturate the membranes and cause precipitation of bilirubin acid within the nerve cell membrane.³³⁻³⁵ This condition represents the classical picture of kernicterus.

Such increases in free bilirubin concentration are usually seen for other reasons, such as in the sick infant, whose albumin binds less bilirubin,³⁶ or in the very premature infant, who because of low serum albumin, will have increased unbound bilirubin levels even at relatively normal serum bilirubin concentrations.³⁶ In addition, bilirubin displacement by drugs, free fatty acids, or other substances may increase the level of free bilirubin and cause increased entry of bilirubin into the brain.²⁹ Again, increased brain blood flow will increase bilirubin passage across the blood-brain barrier, and acidosis will increase the binding of bilirubin to nerve cells within the brain.

A third cause of increased entry of bilirubin into the brain involves albumin-bound bilirubin dianion which can enter the brain if the blood-brain barrier is disrupted. This is probably caused by hypoxemia, hypercarbia, and hyperosmolality; it is also possible that hyperthermia and septicemia can have similar effects.³⁷ Studies have indicated that even with a disrupted blood-brain barrier, on a molar basis more bilirubin than albumin will still enter the brain.²⁹ Furthermore, in this situation, increased brain blood flow will increase brain bilirubin concentrations, and acidosis will increase the binding of the bilirubin acid salt to the nerve cells. The clinical and pathologic significance of this mechanism is still uncertain, although significant effects on neurophysiology^{38,39} and brain energy metabolism,⁴⁰ as well as on behavior,⁴¹ have been demonstrated after blood-brain barrier disruption in the jaundiced experimental animal.

REVERSIBILITY OF BILIRUBIN TOXICITY

Probably the most important aspect of bilirubin entry into the brain and the toxicity this might produce is the question of reversibility of these effects. The reversibility of bilirubin toxicity has been shown in both in vitro studies in experimental animals and in the jaundiced newborn infant. Particularly important for the clinical situation is the demonstration of this reversibility of bilirubin neurotoxicity in the newborn infant;^{13,42} however, this raises the question as to what determines whether bilirubin toxicity will be irreversible. There are no indications that certain bilirubin effects are always reversible. Such factors as the duration of the hyperbilirubinemia (in a healthy term infant) or the presence of acidosis in a sick newborn with respiratory distress syndrome might contribute to irreversible bilirubin effects.

Figure 2 illustrates the situation in the healthy full-term infant. On the basis of the empirical findings that an exchange transfusion at a serum bilirubin level of 20 mg/dL usually prevents kernicterus in an infant with hemolytic disease, this level was considered a fairly sharp limit between safe and dangerous levels of bilirubin, as indicated in Figure 2 (panel A). However, the situation is probably more like the concept depicted in Figure 2 (panel B). There is probably a continuum in which bilirubin toxicity gradually increases with the serum concentration, and this toxicity then gradually becomes irreversible, depending both on the bilirubin levels as well as on other factors.

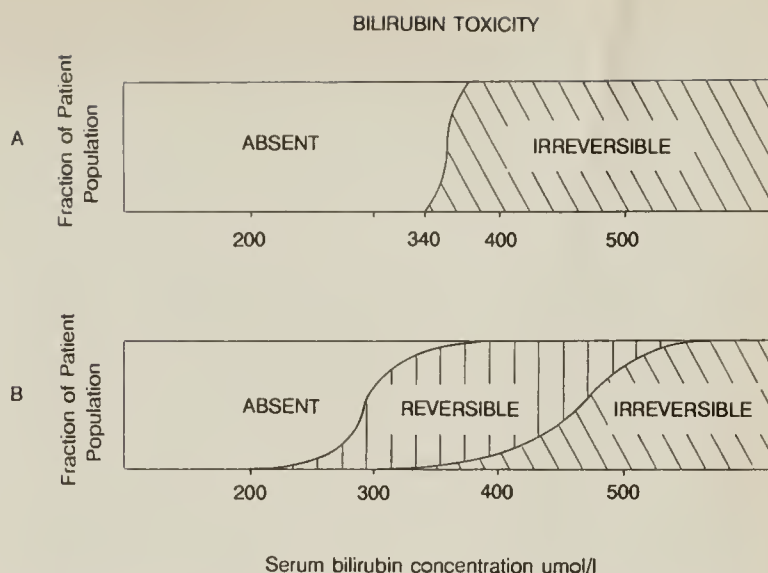


FIGURE 2. Schematic diagram showing the relation between serum bilirubin concentrations and signs of bilirubin toxicity in full-term healthy newborn infants. (A) Old model, with a sharp limit between no toxic effect and irreversible toxicity. (B) Modern view, where there is gradual transition between no clinical effect, signs of reversible toxicity, and irreversible toxicity. A vertical line will indicate fractions of the patient population to be found within the different toxicity regions at different serum bilirubin levels.

In Figure 2, the range of values for which reversible toxic effects of bilirubin might be seen is somewhere between a bilirubin concentration of 200 and 300 $\mu\text{mol/L}$ (12–18 mg/dL). This is based on the general observation of reduced alertness and poor feeding in such infants, as well as on documented effects on auditory BAER,^{13,14} visual evoked responses,¹⁴ and cry analysis.¹⁵ In the same figure, the limit for irreversible bilirubin toxicity has been assumed to be within the range of 300 and 500 $\mu\text{mol/L}$ (19–30 mg/dL). This range was arbitrarily set. However, selection of the lower limit was influenced by our own experience with a deaf child who received an exchange transfusion at a bilirubin level of 314 $\mu\text{mol/L}$ (19 mg/dL). Nevertheless, the limits in Figure 2 should be considered as illustrations of the problem and as strong suggestions being more than recommendations. Susceptibility to irreversible bilirubin toxicity varies tremendously; there probably is a concentration range (200–400 $\mu\text{mol/L}$ or 12–24 mg/dL) in which all types of neurologic outcomes may occur. This makes it impossible to evaluate independent patient risks on the basis of serum bilirubin concentrations alone.

The possibility of beneficial effects of bilirubin in the neonate has recently been emphasized;⁴³ under certain circumstances, it may act as a natural antioxidant. These suggestions have to some extent nourished the speculation that it might be wrong to treat hyperbilirubinemia too aggressively in the newborn, particularly in the absence of hemolytic disease.⁴⁴ However, the possible beneficial effects of bilirubin would probably only be significant in the very sick premature infant, and they should not be used to argue against the routine treatment of hyperbilirubinemia in the otherwise healthy term or near-term infant.

CONCLUSIONS

Recent research has clarified the basic mechanisms of how bilirubin enters the brain. Clinical studies have so

far failed to show any value of the presently known risk factors in predicting bilirubin toxicity in the newborn infant.⁴⁴ However, the fact that bilirubin is a cause of kernicterus in the newborn with severe hemolytic disease is not disputed by anyone. In addition, most clinicians agree that the effects of bilirubin toxicity may be seen in the severely ill premature infant. However, the practical significance of bilirubin toxicity per se is difficult to define in the sick premature infants, in view of the many other, and probably more important, risk factors have that portend later developmental disorders in these infants.³² However, for the full-term healthy infant without hemolysis, it has been suggested that the current treatment regimens are too aggressive in view of the minimal risk for bilirubin toxicity.⁴⁴ Although this conservative policy might be correct for the majority of such infants, it might also be dangerous for a few of them. This fact should stimulate research to clarify the molecular basis for bilirubin toxicity, as well as to identify better indicators for this toxicity than serum bilirubin concentrations alone. Such studies may eventually form the basis for a more rational policy for preventing brain damage caused by bilirubin and providing more specific therapeutic options.

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Cellular basis of bilirubin toxicity

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How does bilirubin act at the cellular level? How does it get there and what does it do? Would this knowledge help us in predicting kernicterus and managing patients at risk? This review of recent information and speculation suggests that we may have to reappraise traditional strategies in managing jaundiced newborns.

HOW DOES BILIRUBIN GET INTO TISSUE

It has long been known, and generally ignored, that acidemia greatly influences the binding of bilirubin to tissue, shifting the equilibrium from plasma to extravascular compartments. The classic study by Bratlid¹ demonstrated a marked difference in partitioning between albumin and red blood cells when the molar ratio of bilirubin to albumin increased and the pH decreased. We recently took a closer look at this relationship and found that, at equilibrium, the concentration of bilirubin in red cells was a direct function of hydrogen ion concentration.² Furthermore, if the hydrogen concentration is extrapolated to zero, almost no bilirubin is taken up by pH-independent mechanisms.

How can these findings be explained? It was initially thought that acidemia displaced bilirubin from albumin, but several studies have shown that binding to albumin is not significantly affected by changes in hydrogen ion concentration within the physiologic pH range.^{3,4} The reason for increasing tissue uptake of bilirubin with decreasing pH must lie in the other half of the chemical equation, namely the interaction of bilirubin with cells.

The linear relationship between hydrogen ion concentration and cell binding indicates that a single proton (or hydrogen ion) is added to bilirubin in the binding process.² There are two possible explanations for the hydrogen ion dependence of tissue binding for bilirubin. Either bilirubin is converted from the bilirubin dianion (B^{2-}) to monovalent anion (BH^{2-}), or it is converted from the monoanion to acid (BH_2) form. Most evidence indicates that the bilirubin in plasma exist predominantly as the dianion,^{5,6} comprising about 98%–99% of bilirubin in aqueous solution at physiologic pH. Conversion of the dianion to monoanion is consistent with tissue uptake studies.² In 1974, it was shown that toxicity to cultured L929 fibroblasts increased with lower pH.³ However, when these data are transformed from free bilirubin exposure to free bilirubin monovalent anion exposure, the LD_{50} is identical at both pH 7.4 and 7.0. Others have recently challenged this conclusion, however, and have provided evidence that the pK of bilirubin side groups is alkaline in aqueous solutions.^{7,8} This would produce a mixture of bilirubin acid states at physiologic pH; the bilirubin acid concentration would

increase with decreasing pH, but not in direct proportion to hydrogen ion concentration. Measurement of the pK values for bilirubin in aqueous solutions is complicated by the low solubility of bilirubin, and a definitive determination has yet to be accomplished.

Hydrogen ion dependence of membrane binding appears to be a general phenomenon. Thus, we can estimate the relative bilirubin load to tissue in equilibrium with plasma bilirubin by measuring the free bilirubin concentration and blood pH. In most cases, the free bilirubin level is a function of the bilirubin/albumin ratio, and these values can be obtained in any clinical laboratory. Tables I and II list calculated serum bilirubin concentrations that should yield the same tissue concentration at varying pH and concentrations of albumin on the basis of changes in the monovalent anion concentration. Assumptions using bilirubin monoanion to acid conversion produce slightly higher tissue concentrations at lower pH. These tables make no assumption of appropriate exchange level, but compare relative risks using commonly held indications for exchange transfusion as a reference.

The data listed in Table I are also depicted in Figure 1. Conditions are compared for an infant who has a bilirubin level of 20 mg/dL, an albumin of 3.3 g/dL, and a normal pH of 7.35. For example, compared with the reference patient, an infant with an albumin of 2.4 g/dL and a pH of 7.3 will have the same pressure for bilirubin deposition in brain when the serum bilirubin is 14 mg/dL. Table II uses an exchange level of 24 mg/dL as a reference. These tables assume normal intrinsic binding of albumin, which may be altered in sick babies,⁹ and they also assume that there are no competing drugs or endogenous competitors such as fatty acid present in plasma. Furthermore, variations in blood-brain barrier permeability, variations in pH within the brain, and variations in susceptibility of target neurons within the brain will limit the precision of any serum measurement in predicting the risk for kernicterus.

Notwithstanding these limitations, the influences of albumin concentration and hydrogen ion concentration of bilirubin partitioning within the body are of such magnitude that epidemiologic studies relating clinical outcome only to levels of total bilirubin or unconjugated bilirubin will yield, at best, imprecise and possibly misleading predictive data. Such lack of precision would most likely occur when studying populations with varying albumin concentrations and brain pH such as premature infants and newborns with severe hemolytic disease. The pH dependence of bilirubin binding to tissue emphasizes the need to evaluate the arterial blood gas in a severely jaundiced baby and to correct acidosis. This is particularly important in respiratory acidosis, since CO_2 equilibrates rapidly in the brain. In addition, hypercap-

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TABLE I. Serum Unconjugated Bilirubin Concentrations Producing the Same Tissue Bilirubin Concentration at Different pH and Albumin Concentrations* (Reference Condition: Serum Bilirubin, 20 mg/dL; Albumin, 3.3 g/dL; and pH 7.35)

pH	Albumin Levels (g/dL)						
	1.6	2.0	2.4	2.8	3.2	3.6	4.0
7.5	10.7	13.4	16.0	18.7	21.4	24.0	26.7
7.4	10.0	12.6	15.1	17.6	20.2	22.6	25.1
7.3	9.3	11.7	14.0	16.3	18.7	21.0	23.3
7.2	8.6	10.7	12.9	15.0	17.2	19.3	21.4
7.1	7.8	9.7	11.7	13.6	15.6	17.5	19.5
7.0	7.0	8.7	10.5	12.2	13.9	15.7	17.4
6.9	6.2	7.7	9.2	10.8	12.3	13.9	15.4
6.8	5.4	6.7	8.1	9.4	10.7	12.1	13.4

*Listed values are based on normal serum albumin-binding characteristics and do not consider complications of competitors (eg, drugs or renal failure), brain susceptibility (eg, hypoxia), status of the blood-brain barrier, or cerebral pH. Unfortunately, variations in permeability of the blood-brain barrier, in microenvironmental pH, and probably in susceptibility of target nuclei in the brain, will limit the precision of any serum measurement predicting risk for kernicterus.

nia increases cerebral blood flow and, hence, increases bilirubin delivery to the brain.^{10,11}

HOW DOES BILIRUBIN POISON THE BRAIN?

The observation that reversible changes in the auditory evoked response may reflect early bilirubin toxicity suggest that mechanisms involved in neurotransmission may be an early target for bilirubin poisoning. High levels of bilirubin inhibit neurotransmission in hippocampal slices.¹² Bilirubin also inhibits phosphorylation of synapsin I, which is a critical step in neurotransmitter release.¹³ Statistically significant inhibition of phosphorylation occurred at a bilirubin concentration of 10 $\mu\text{mol/L}$, but marked inhibition occurred only at levels of about 40 $\mu\text{mol/L}$. At a concentration of 137 $\mu\text{mol/L}$, bilirubin inhibits tyrosine uptake and dopamine synthesis in striatal synaptosomes (Cashore W, personal communications, 1990). However, much lower levels of bilirubin, 10 $\mu\text{mol/L}$, produce a marked change in membrane potential in synaptosomes.¹⁴ Similar thresholds of bilirubin have been reported for uncoupling oxidative phosphory-

lation in isolated mitochondria,¹⁵ where bilirubin has been shown to increase inner membrane conductivity and translocate protons.¹⁶ Severe metabolic disturbances in brain occur in animals with hyperbilirubinemia after osmotic opening of the blood-brain barrier and probably represent diffuse mitochondrial dysfunction.^{7,8} Mitochondrial dysfunction is most likely an important element in the pathogenesis of irreversible bilirubin encephalopathy.

The molecular mechanisms of bilirubin toxicity remain a mystery. Brodersen and Stern¹⁹ proposed that tissue uptake of bilirubin involves the precipitation of the bilirubin acid in phospholipid membranes. In contrast, the monovalent anion hypothesis²⁰ proposes that reversible complexes of bilirubin monoanion and membranes predominate in the development of bilirubin encephalopathy. The monovalent hypothesis helps to explain why tissue-bound bilirubin is readily extracted during exchange transfusion, and why early toxicity, including alteration of the brain stem auditory evoked response, is reversible.²¹ Interaction of the bilirubin monoanion with membranes could explain depolarization and uncoupling. When the monoanion enters the lipid core of the membrane, it would accept a second proton, making it more lipid soluble. This proton would be released as bilirubin emerges on the opposite surface (Fig 2). Given sufficient fluidity in the immature membrane, bilirubin might also pass as the monoanion. This would give bilirubin the property of a protonophore, enabling it to shuttle hydrogen ions across membranes and short circuit hydrogen ion gradients.

Maintenance of a transmembrane hydrogen ion gradient is critical for oxidative phosphorylation in mitochondria, and may be important in controlling neurotransmitter release in synapses. If this is true and if membrane fluidity plays a crucial role in bilirubin toxicity, there may be pharmacologic ways of altering membranes. For example, cholesterol stabilizes membrane order, whereas benzyl alcohol, a preservative recently implicated in an epidemic of kernicterus,²² greatly increases fluidity.²³ It should be noted that frequently quoted studies discounting the value of binding tests²⁴ and other risk factors²⁵ in predicting kernicterus in sick premature infants were conducted during a time when many of these infants were inadvertently exposed to benzyl alcohol.

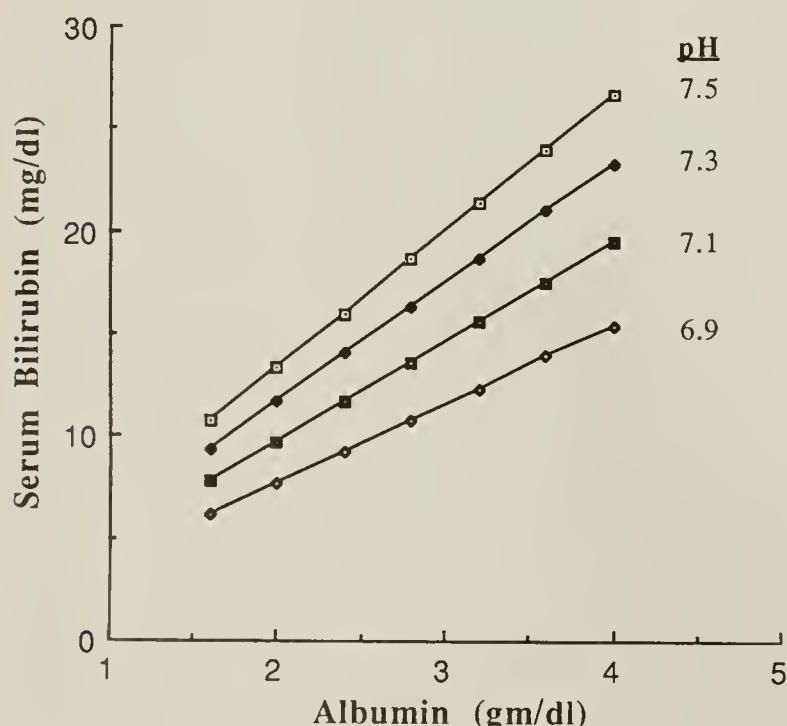


FIGURE 1. Serum bilirubin concentrations yielding the same tissue bilirubin load at varying pH and serum albumin concentrations. The reference "exchange transfusion level" of 20 mg/dL occurs with an albumin level of 3.3 g/dL and pH of 7.35.

TABLE II. Serum Unconjugated Bilirubin Concentrations Producing the Same Tissue Bilirubin Concentration at Different pH and Albumin Concentrations* (Reference Condition: Serum Bilirubin, 24 mg/dL; Albumin, 3.3 g/dL; and pH 7.35)

pH	Albumin Levels (g/dL)					
	2.0	2.4	2.8	3.2	3.6	4.0
7.5	15.4	18.4	21.5	24.6	27.6	30.7
7.4	14.8	17.8	20.8	23.7	26.7	29.7
7.3	14.2	17.1	19.9	22.8	25.6	28.5
7.2	13.5	16.3	19.0	21.7	24.4	27.1
7.1	12.8	15.3	17.9	20.4	23.0	25.5
7.0	11.9	14.3	16.7	19.0	21.4	23.8
6.9	11.0	13.2	15.4	17.5	19.7	21.9
6.8	10.0	12.0	14.0	16.0	18.0	20.0

*See footnote to Table I.

It is possible that our tentative assignment of an acidic pK for bilirubin is wrong, and that tissue binding involves bilirubin acid-lipid complexes.⁷ If so, bilirubin would not function as a protonophore but could still alter membrane function by disordering the lipid environment of membrane proteins. The activities of many transmembrane protein channels, such as Ca^{++} , Mg^{++} , and ATPase,²⁶ are very sensitive to their lipid environment.

Finally, although tissue binding of bilirubin depends primarily on lipid-bilirubin complexes, it is possible that bilirubin toxicity results from specific binding to receptor sites on enzymes. For example, it was found that bilirubin competitively inhibits purified mitochondrial malate dehydrogenase with a rather low $k_{\text{(inhibition)}}$ of 2 $\mu\text{mol/L}$.²⁷ Malate dehydrogenase participants in the malate-aspartate shuttle responsible for the transport of reducing equivalents across the inner membrane of mitochondria. Inhibition of this enzyme would result in the accumulation of NADH in cytoplasm, a high NADH:NAD⁺ ratio and, secondarily, a high lactate:pyruvate ratio as can occur in experimental bilirubin encephalopathy.¹⁸

“WINDOWS OF VULNERABILITY”

The developing brain appears to have certain windows of vulnerability to toxic insults. As the brain evolves from an immature organ to a more mature structure, susceptibility to bilirubin or other insults may change. This principle is illustrated in some elegant experiments performed in the Gunn rat,^{28,29} which is an animal with hyperbilirubinemia produced by congenital absence of bilirubin glucuronyl transferase. A major target neuron in the Gunn rat is the Purkinje cell, and the target organ is the cerebellum, resulting in severe hypoplasia. Cerebellar growth and development is thought to be triggered by an outburst of Purkinje dendritic activity on about day seven of life. By exposing rats to phototherapy on specific days, the serum bilirubin concentration was temporarily decreased. Exposure on day seven alone greatly minimized damage both to Purkinje cells and cerebellar development.²⁸ In contrast, other studies using a displacing agent found that bilirubin staining, which occurs more in other regions of the cerebellum, was most intense on day 15.²⁹

This great dependency of site and nature of bilirubin toxicity on stages of development may explain why very immature infants do not develop a classical picture of kernicterus. In the Dutch Perinatal Study of very small premature infants,³⁰ there was a bilirubin dose-dependent increase in neurologic (mostly motor) deficits at two years of age. However, there was no increase in the neurologic deficits commonly associated with bilirubin toxicity. It is quite possible that the spectrum of bilirubin injury in the immature human brain is unique and that underlying developmental, as well as metabolic states of the brain influence the susceptibility of various brain regions to bilirubin exposure.

CONCLUSIONS

The pathogenesis of bilirubin encephalopathy is a multifactorial process that requires a critical level of free bilirubin acid or acid salt, access to brain by permeation of the blood-brain barrier, and the presence of susceptible neurons. The latter may be influenced by cell membrane composition, metabolic state, and stage of brain development. From a clinical viewpoint, measurement of total or indirect bilirubin as the sole indication for therapeutic intervention in a jaundiced newborn should provide the least reliable index of risk for

Bilirubin Transport Across Membranes

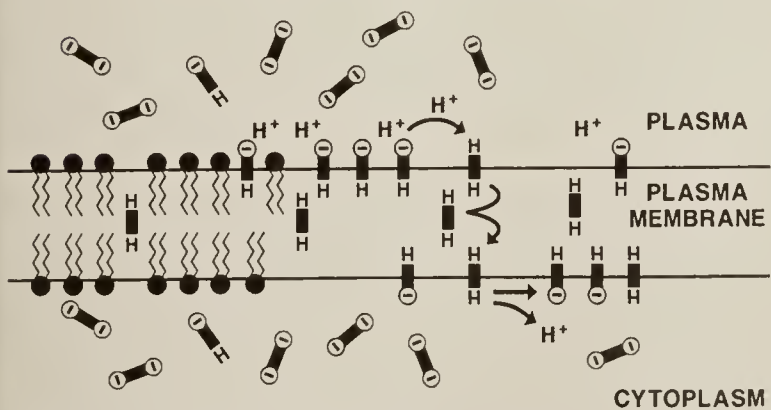


FIGURE 2. Proposed mechanism of bilirubin transport across membranes, according to the monovalent bilirubin hypothesis.^{2,26} The relative hydrophobic mono-anion concentrates at the surface, facilitating addition of another hydrogen ion to form the bilirubin acid which enters the core of the membrane. The hydrogen ion is released as the bilirubin molecule emerges at the cytoplasm-membrane interface. The box gives typical values for unbound bilirubin concentration (UBC) and different subfactions (B^{2-} , BH^- , BH_2) in moles/liter expected at pH 7.4 with a total serum bilirubin level of 250 to 340 $\mu\text{mol/L}$ (15 to 20 mg/dL).

kernicterus. Assessment of risk, with respect to serum values, should involve consideration of the bilirubin: albumin ratio and blood pH. Guidelines for interventions are suggested that estimate comparative risk using the assumption that the tissue bilirubin load is determined by the concentration of free bilirubin monovalent anion.

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Historical perspective and a proposal for forensic medical services in New York State

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On March 23, 1990, the New York State Commissioner of Health, Dr David Axelrod requested Dr Charles Vacanti, Chairman of the Board for Professional Medical Conduct, to convene a special committee to explore the development of standards for forensic pathologists serving as medical examiners. The impetus for this request was Dr Axelrod's review of the Hearing Committee's report in the matter of the State Board for Professional Medical Conduct vs Elliot M. Gross, MD, Chief Medical Examiner of New York City (March 23, 1990). The Commissioner was concerned with a lack of professional standards for forensic pathologists and different approaches to the autopsy protocol by two key witnesses who were nationally recognized experts in the forensic pathology field. Divergent opinions regarding areas such as classification of manner of certain deaths (undetermined, pending investigation), completeness of reports, the role of photography, blood alcohol determinations, bullet wound powder deposit examinations and bullet path studies, and the role of X-rays, were apparent. The different views expressed by these two experts called into question the roles of traditional and perhaps outdated standards measured against higher standards that reflect advances in the discipline of forensic pathology. Dr Axelrod requested that a special committee conduct an inquiry as to what standards should apply and was concerned that the absence of agreed-on professional standards should not be viewed as a license for negligent practice or abdication of governmental or social responsibilities in any branch of medicine.

COMMITTEE ACTIVITY

Dr Vacanti convened a committee consisting of himself as Chair, Dr Albert M. Ellman, Dr William A. Stewart, Dr John T. Prior, Dr John H. Morton, Rev. Edward J. Hayes, and Dr Charles S. Hirsch (Chief Medical Examiner, New York City). The committee was assisted by Kathleen M. Tanner.

At the first meeting on May 9, 1990, it was apparent that a very complete manual entitled *Standards for Inspection and Accreditation of a Modern Medicolegal*

Investigative System already existed.¹ The manual was prepared and sponsored by the National Association of Medical Examiners and the second edition was published in February of 1988. These standards were thought to represent the *minimum* for an adequate medicolegal system with an objective to develop and document a viable and workable law under which the medical examiner or coroner functions. The manual includes guidelines for physical facilities, scene investigation, proper identification, chain of evidence preservation, statistics and budget record keeping, and autopsy procedure techniques. The publishers of the manual, the National Association of Medical Examiners, can provide an inspection team that is available to accredit any medical examiners office on a request.

At the May 9 meeting, the Committee was in agreement that although this manual represented constructive guidelines defining the quality of services rendered by a medical examiner or coroner, there existed a variety of other serious deficiencies in the field of forensic pathology in the state. These included the qualifications and performance of coroners, regional variations in forensic investigators between upstate and downstate locations, lack of provision for consultative services, particularly in small communities, lack of qualified forensic pathologists in the state, inadequate resources and fiscal allocations, relationships with county governments, health departments, sheriff's departments or other criminal justice agencies, and responsibilities of the medical examiner with regard to acquired immunodeficiency syndrome, child abuse, communicable diseases, safety hazards, hospital and home deaths.

It is of interest that many of these problems were addressed in 1987 by an ad hoc committee of the New York State Public Health Council. Their report was prepared by six physicians (none of whom were forensic pathologists) and adopted on October 23, 1987. The report presented discussion of problem areas and recommended both immediate and long-term actions.

A second meeting of the committee was held on July 11, 1990 in the office of the Chief Medical Examiner of New York City. All the medical examiners in the state were invited. The committee made the following recommendations to Dr Axelrod regarding death investigations in New York State.

Address correspondence to Dr Prior, County of Onondaga, Medical Examiner, 230 West Onondaga Street, Syracuse, NY 13202.

DEATH INVESTIGATIONS IN NEW YORK STATE

New York State has in its 62 counties and boroughs a wide variety of mechanisms by which death investigations are accomplished. Historically, the coroner has been the officer by statute defined as death investigator to whom responsibility is delegated for making the determination of cause and manner of death in those instances where state interests supervene private ones. The legal background of the coroner's office has its origins in English law introduced by the Norman Kings. A death investigative office was eventually established with the Anglicized name of coroner, derived from the term meaning "an officer of the crown." In the United States this became an elective office with the official duty to effect death certification of deaths of suspicious or non-natural origin. Qualifications for coroner have been eligibility to vote and no mandated training or certification has been demanded in New York State. Some coroners have been physicians with a few having pathology, or even forensic pathology, specialty training, but the majority have been lay persons without formal training in death investigation.

Over the years, numerous accommodations evolved to circumvent the limitations of training and funding that plagued coroners' offices. In 1918, the position in New York City was converted from an elective coroner to an appointed medical examiner from which followed improvements in the quality of professional staff and support services, after which New York became, for years, a model for the nation's death investigators. Upstate counties with larger cities followed suit.

With the advent of more technically sophisticated medical examiner's offices around the state, referral of case material began to occur on a sporadic and pragmatic basis in response to the increased technical expertise that these offices possessed. These referrals were, however, severely constrained by the problems of finance and logistics so that only some of the coroner's offices availed themselves of the increasing expertise present within the state.

While distinguishing the fundamental differences between the lay coroner and the medical examiner, further distinction must be made between medical examiners with specific training in death investigation and medical examiners with other backgrounds. Among the 17 counties where medical examiners are in the office today in the state, nine have as chief a person certified by the American Board of Pathology in the specialty of forensic pathology. The remaining counties have physician chiefs whose qualifications range from general practitioner to hospital pathologist. Thus, qualifications, even between the medical examiner's offices, varies considerably.

All the differences made apparent above are expressed as a variable capacity for and quality of death investigation across the state, with marked differences in physical plant and support systems. Each county, autonomous in its choice and support of a death investigator, creates a system perceived as adequate for its own needs and often determined by persons of limited or with no specific expertise in death investigation.

Oversight and quality assessment are, except through the vagaries of the tort and liability statutes, by crisis and

occasional outcry without planned direction. In response to the question of cost and quality, there have been, over the years, proposals for regionalization of services and for superimposition of centralized authority. So far, efforts to impose statewide authority and stewardship have failed on the grounds of either political unacceptability or cost. Thus, any hope for progress must include a package of structure and finance not perceived as a major burden by the community served.

Just as, for many political reasons, New York State can be divided into upstate and downstate regions, so too can the state be divided when characterizing the provision of death investigative services.

The downstate area is composed of two counties of Long Island, five boroughs of New York City, and the immediately adjacent counties of Rockland and Westchester. Upstate differs from downstate in having a much lower population density with many counties having fewer than 100,000 inhabitants and some having fewer than 50,000. Downstate is primarily urban and suburban whereas upstate often has large distances between towns and accessible services. Economic differences allow downstate counties to fund medical examiner's offices to the point of self-sufficiency, whereas only three upstate counties, Erie, Monroe, and Onondaga, can claim to have full forensic medical services available.

For the upstate counties, the above has lead to some intercounty working relationships developed on an ad hoc basis. There are frequent case referrals to the larger medical examiner's offices from the more rural counties with a few formal contracts between counties. There is, however, no guarantee that decisions to refer cases will be made by properly informed or trained persons, leaving the final outcome of a given investigation not in the hands of a qualified forensic pathologist, but with the uncertain denominator involved in the investigation in a neighboring or close by county. Under these circumstances, no demands can be made by the more trained investigator of the less-trained investigator except on a purely collegial basis with the immediate right of refusal of cooperation by the less-trained person. Death certification in a coroner county is by the coroner, and if the coroner is not an MD, in conjunction with a physician.

It is time to require a certain minimum training of all coroners, coroner's physicians and medical examiners and to expect a commensurate level of performance. A central oversight authority that is politically and functionally workable, must be developed as well as investigative standards, case referral mechanisms, facility standards, individual performance standards, and training minima to include initial training and continuing medical education.

A past proposal for central coordination included the suggestion of superimposition of a State Medical Examiner on the existing county based systems. This possibility was strongly opposed and would in all likelihood fail to gain approval today. The creation of a central bureaucracy sufficient to control all death investigations out of one office would be very expensive and extremely cumbersome. Consider that the collation of upstate death certificate data alone costs close to \$2 million per annum. In addition, the replacement of the vagaries of

62 county policies by the idiosyncrasies of a single person could as easily do harm as do good, should the office holder not be adept at recognizing the variability of need for different localities.

Most likely to succeed would be a commission under whose aegis most questions related to standards and performance could be addressed in a way that would allow all jurisdictions and interested parties to understand that their diverse needs have been seriously addressed before any institution of statewide policy. The commission would also function in an advisory capacity and express with authority the fiduciary requirements which county and state legislative bodies would have to address and put in place.

RECOMMENDATIONS

From the viewpoint of medical examiners, one can propose a committee representative of law enforcement, legal, and medical communities, which could function to set and review policy in a fashion acceptable to all users of these services.

We propose a commission of nine members with three year terms. The chief medical examiner, coroner, and medical school representatives would be able to succeed themselves only once and would be chosen by gubernatorial appointment from lists of names presented by the Medical Society of the State of New York, New York State Association of County Coroners and Medical Examiners, and the associated medical schools of New York, respectively. An attempt to maintain an upstate and downstate distribution should be considered. Once off the commission for a term, eligibility would resume. The first commission appointments would have a 50% planned renewal rate to ensure continuity for the start-up period.

The commission would meet at least quarterly and would do business in committee between quarterly meetings. Responsibility would include a regular review of policy in all jurisdictions, the establishment of minimum facility standards (such as the National Association of Medical Examiners guidelines), and the establishment of minimum standards governing investigation, death certification, training and the performance of autopsies. Although each county could initiate policy internally, review by the commission would be mandatory.

Finally, the commission would encourage appropriate referral for cases to consultants or from the less-equipped rural counties to counties with greater resources. This latter activity would, in all probability, dictate some determination of fee schedules and might

Table I. Commission Scope of Authority

Shall promulgate minimum standards for facilities, training, staffing, and work performance in all aspects of death investigation in coroner and medical examiner offices.
Shall be able to encumber funds for commission meetings and committee work, and may disburse funds if made available by legislative action or grants.
Shall report to the legislature annually on requirements for the death investigative system in New York State.

TABLE II. Suggested Medical Examiner's Commission Membership

Standing Members
1 Department of Health
1 Division of Criminal Justice Services
1 Public—Ombudsman
3 Chief Medical Examiners, certified in forensic pathology
1 Coroner—NYSACCME Certified
1 Medical Society of State of New York
1 Physician representative of Association of Medical Schools of NYS

Appointees shall have staggered terms and have 3-year tenure with option for a single renewal. Eligibility for reappointment will then recur after one term not on the commission.

The first appointed commission shall have at least half the members reappointed for a second term.

only take place if the system as a whole were incorporated into a state funding mechanism with reimbursement of the counties for additional expenses of investigation.

How would adherence to the commission's envisioned standards be encouraged in today's tax climate? With the adoption of written minimum performance standards, the smaller counties would be forced into one of two options: complete independent county-based service at high cost, or referral at much lower cost. Thus, the cost of regulation would not devolve directly on the state. In many ways, then, the establishment of a largely voluntary standard through a state funded commission would, over a period of a few years, lead to a much greater degree of consistency and an improvement in performance of death investigations, especially for the upstate counties.

The geographic and demographic realities of regional forensic services in upstate New York are that Erie, Monroe, and Onondaga are the only available offices with certified forensic pathologists, in house toxicology, and laboratory support. Each of these offices can potentially establish a local referral region of up to about 100 miles distance, thereby providing services for western and central New York State. However, staffing levels must be developed in proportion to the level of activity. Eastern New York State is short on forensic pathologists and has no referral medical examiner system available. Albany county is served by coroners and the state may have to provide a nidus of qualified persons if a referral center for that region is to be established. Closer to the downstate counties, there are no offices seeking to regionalize since the present systems already are busy and threatened by overload if regional referral is mandatory. An Albany office would considerably reduce such pressures if referrals were accepted. With commission adoption of standards, this problem would quite likely find its own solution over a period of a few years.

The first step, if progress is to be made, will be to reach agreement on the composition and authority of a medical examiner's commission. A funding mechanism must be identified to allow the commission to function. Although the commission is not seen as the bursar of a statewide system, there are secretarial and meeting expenses which must be met for the commission to do its review work.

A medical examiner's commission can be at work almost immediately by its defacto establishment as long as the commission is recognized as being composed of persons with sufficient expertise to speak with authority on the question of standards. The assistance of the New York State Department of Health, the widespread publication of commission standards, and acceptance of

these standards by one or more of the state's agencies, would go a long way toward essentially voluntary compliance.

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A community-based hospice program

PETER ROGATZ, MD; FRED SCHWARTZ, MD; JEANNE DENNIS, ACSW

For almost eight years the Visiting Nurse Service (VNS) of New York has operated a palliative care program for patients who are suffering from advanced illnesses with limited life expectancy. The program was formally certified as a hospice under Medicare more than three years ago. Experience to date has been rewarding for patients and their families and well as for the staff.

How hospice programs function in this country is not widely understood, even among professionals. This lack of information deprives many patients and families of the very valuable supportive care they might receive from hospice programs and deprives physicians of access to important resources, which they might use on behalf of their patients. A brief report of the experience of the VNS hospice program is presented here.

BACKGROUND

The hospice had its inception in modern times in Great Britain in 1967, when Dr Cicely Saunders founded St. Christopher's Hospice. Her emphasis on effective control of symptoms during terminal illness, interdisciplinary care of both patient and family, continuity of care in various settings (including home care), and support of bereaved family members became the keystone of a movement that was to spread internationally. It became the basis for standards adopted in this country by the Joint Commission on Accreditation of Health Care Organizations and by the National Hospice Organization (NHO).¹

The first hospice in the United States was founded in 1974 in New Haven, Connecticut. Like its progenitor in England, it was institutionally-based. However, as the hospice movement gradually took root and spread throughout the United States, the value of caring for terminally ill patients in their own homes became increasingly apparent. Some hospices in this country are affiliated with hospitals, nursing homes, or other institutions, functioning primarily as extensions of these institu-

tions. Others are independent, community-based agencies, and some are affiliated with home health agencies. Among this latter group is the VNS hospice care program.

Growth of the hospice movement in the United States has been substantial. Five years after the founding of the first hospice in New Haven, there were 75 such programs throughout the country; this number increased more than tenfold to a total of 825 by 1982 and almost doubled again within the next few years.² According to a study carried out for the NHO, there were 1,529 operating hospices in this country in the year 1989.³ Of these, 41% were independent, 30% were operated by or directly affiliated with hospitals, 23% were operated by home health agencies, and 5% by other organizations. Of the total, 96% of the programs were not-for-profit and 4% were operated for profit. There were 996 Medicare-certified hospice programs, representing just under two-thirds of the total. Altogether, some 187,000 patients were served by hospice programs in this country during the year 1989, of whom approximately 113,000 were served under the hospice benefit of the Medicare program. The average length of stay for patients in Medicare-certified hospice programs was 58 days.³

BACKGROUND OF THE VNS HOSPICE PROGRAM

The history of the VNS goes back to 1893, when Lillian Wald and Mary Brewster established a service to provide care at home to indigent immigrants. The agency has grown and evolved over the years in ways that surely could not have been foreseen a century ago.

Today the VNS is an "umbrella" organization embracing a family of agencies that includes VNS Home Care (a certified home health agency), Partners in Care (a licensed agency providing home health aide, LPN, and RN services, and Family Care Services (providing home attendant services and Meals-on-Wheels). Among the programs operated by VNS are those for general adult care, maternal/child health and pediatrics, long-term care, community mental health services, care for patients with the acquired immunodeficiency syndrome

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(AIDS), a "high-tech" program (offering intravenous therapy for total parenteral nutrition, hydration, continuous pain control, and administration of antibiotics and chemotherapy), and hospice care.

The VNS hospice program originated in 1984 but did not actually assume the name "hospice" until after Medicare certification four years later. It is the only hospice program operated by a certified home health agency in New York City. In the three years since its Medicare certification, the program has provided care for more than 1,000 patients. Currently, the program has an average daily census of approximately 90 with the projection of a total of 650 patients to be cared for during the year 1991.

The great majority (~90%) of patients cared for by the VNS hospice program have terminal cancer. The distribution of diagnoses recorded during the period January through June 1990 reveals the following primary cancer sites: lung 19%, colon 12%, prostate 9%, breast and pancreas 6%, each and all other sites (including lymphomas) 38%. Diagnoses other than cancer included various disorders of the cardiac and pulmonary systems (7%) and AIDS (3%).

Although the number of AIDS patients cared for by the hospice program in 1990 was small (only 12 of a total of 465 admission during the year), the number of patients with AIDS cared for by VNS Home Care as a whole (through programs other than hospice) was quite substantial, approximately 2,750 patients of a total of some 70,000 admissions during the year 1990.

It is not surprising to find that cancer patients predominate in most hospice programs. The general practice is to set a life expectancy of six months or less as one of the requirements for admission to hospice programs. Life expectancy among cancer patients tends to be more predictable than among patients with other illnesses, so physicians are more likely to refer patients with cancer. It is also not surprising that patients with AIDS, in spite of the grim prognosis associated with that diagnosis, tend to elect hospice care less frequently than other patients with equally poor prognoses because there is a steady flow of potential new treatments for AIDS and thus these patients often seek aggressive treatment in preference to palliative care.⁴

DESCRIPTION OF THE PROGRAM

The VNS hospice program exists to offer terminally ill patients and their families the option of spending the final weeks and months of their lives together, in the comfort and privacy of their homes. The intent of the program is to provide care that is fully responsive to each patient's clinical needs and personal wishes. Central to the design of the program is the concept of a team of professionals and volunteers, working together to provide physical, psychological, social, and pastoral support for both patient and family. This interdisciplinary team develops a plan of care that is carefully designed to meet each patient's particular needs and is respectful of his or her values, culture, and personal choices. Throughout, the focus of care is on maintaining the patient's quality of life.

The VNS hospice program is organized into four teams, serving patients who live in Manhattan, Bronx, Queens, and Brooklyn. Each team meets weekly to discuss and evaluate the patient's plan of care, clinical status, and the family's adjustment to and ability to cope with the patient's illness. The team, headed by a nurse manager, includes the following:

- Professional nurses (carrying an average caseload of ten patients per nurse)
- A medical or psychiatric social worker
- A physician with experience in management of terminally ill patients and particularly patients with severe pain
- Pastoral/spiritual counselors (clergy experienced in hospice care and counseling)
- Nutrition consultant
- Certified home health aides
- Volunteers
- Bereavement counselor

Various other services, beyond those represented by specific team members, are also available, including physical, speech, occupational and music therapy. Medical equipment and supplies are provided, as well as medication related specifically to the patient's terminal illness. Nurses and physicians are on-call and available 24 hours a day, seven days a week, 365 days a year.

The following are criteria for admitting patients to the VNS hospice program:

- A life expectancy of six months or less
- Need for palliative care rather than curative treatment
- A family member or friend who is willing to provide ongoing assistance for the patient between visits by members of the hospice team (this person does not need to reside with the patient)
- Desire by the patient to be cared for at home.

Staff training focuses on personal awareness of death, listening skills, understanding of family dynamics, role changes in crisis situations, pain, and symptom control, nutrition and food preparation, separation behavior and the grief process. Volunteers are educated to work with the dying and their families and are asked to make a significant commitment of time to the program.

An important advantage of providing hospice care under the auspices of a home health agency is that patients do not need to relinquish their personal physicians. These physicians review hospice plans of care and receive regular reports from the hospice team. However, patients may choose to use the hospice team physician as their primary physician, particularly if they are no longer able to get to their physician's office. Since the hospice team physician has expertise in symptom control and particularly pain management, personal physicians may ask the hospice physician to assume management of specific clinical problems.

When hospitalization is required, the patient is admitted to one of several hospitals with which VNS Hospice maintains formal arrangements. In our experience, hospitalization has been infrequent and brief: less than 2% of all patient days in our program are provided in an

in-patient setting. The great majority of patients in the program have expressed the wish to die at home, and the VNS program has generally been able to achieve this result. Following a patient's death, close attention is paid to bereavement follow-up with family members over an extended period of time, usually until after the first anniversary of the patient's death.

A brief example of the team approach to patient and family care is a 49-year-old woman with melanoma of the right leg, which had metastasized to the shoulder, groin, and lungs. Her husband contacted the VNS hospice program while his wife was an in-patient at a major Manhattan medical center and receiving continuous intravenous infusion of morphine sulfate. The patient wanted to spend her remaining time at home with her family in Queens, as independently as possible. On the suggestion of the hospice team physician, while the patient was still hospitalized, the patient was successfully converted to oral morphine sulfate, 160 mg every 4 hours, with excellent pain control and no side effects, and was discharged two days later. She was well enough after discharge to take a five-day vacation with her husband to the Caribbean. The hospice nurse made two home visits per week dealing with all pertinent issues including that of body image, as the advancing melanoma caused increasingly severe physical disfigurement. The physician noted on one of his home visits that two of her toes were becoming gangrenous, and the social worker dealt intensively with the patient in grappling with the decision as to whether or not a vascular surgeon should be called in, a course which she ultimately declined. The pastoral care counselor held a family service in which her two grown children, who had distanced themselves from their mother because of their intense grief, participated in an anointing ceremony at which their love was openly shared. She died peacefully at home with her family at her bedside three months after acceptance in the hospice program.

SOME SPECIAL CONSIDERATIONS

Referrals may be made by a patient's physician, a hospital discharge planner, nurse, or social worker, a community agency, or the patient's own family members or friends. When a referral is made by someone other than the patient's personal physician, that physician is always contacted to obtain his or her active participation in evaluating the appropriateness of the patient for hospice care. In spite of a growing number of physicians

and other professionals who make referrals, the hospice staff recognize that many patients would benefit from earlier referral for maximum control of physical symptoms and for the psychological, social, and spiritual support of patient and family as the patient goes through the death process. Therefore, when a reasonable estimate can be made that death is expected in a matter of three to six months, a referral for home hospice care can be made.

Hospice services are covered (without co-payment) by Medicare, Medicaid in some states (New York being one), Blue Cross/Blue Shield, and most private insurance coverages. Reimbursement often falls short of reasonable operating costs for the type of complex, comprehensive, interprofessional care provided by hospice programs. The VNS hospice has incurred an operating deficit each year which must be covered by grants or philanthropy; other hospice programs have had a similar experience.

It is somewhat ironic to be confronted with inadequate reimbursement because there is evidence that hospice care provided at home is less costly than alternative types of care. In this regard, Benjamin has observed that "the last months of life represent a disproportionately expensive period in health care terms and one for which the cost-savings potential is high. Although the findings are somewhat mixed, the literature generally supports the conclusion that the home care hospice model is less costly than non-hospice care, while the hospital-based hospice model seems to yield little or no savings. The low costs of the home-based model are directly attributable to the relatively low utilization of inpatient days by home care patients."⁴

Regardless of current reimbursement limitations, the VNS is fully committed to its hospice program. The rewards of this program, not only for patients and their families, but also in terms of personal satisfaction for staff (professional, paraprofessional and volunteer), are great and deserve to be continued and expanded. The Visiting Nurse Service of New York is committed to doing exactly this.

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Pelvic fracture following karate kick

RICHARD B. BIRRER, MD, TIMOTHY ROBINSON, MD

The Martial Arts connotes a variety of disciplined training styles that teach fighting techniques to protect oneself both offensively and defensively in confrontation. Some forms focus mainly on upper body movements (eg, Aikido), others on lower body movements (eg, Tae Kwon Do), and most on combination movements (eg, Karate). The patient presented here suffered a serious injury to the pelvis as a result of a kick to the patient's groin.

CASE REPORT

A 27-year old man presented to the emergency department of the Catholic Medical Center of Brooklyn & Queens, Inc, 1990 with a chief complaint of pain in his right groin. He reported having been side-kicked in the right anterosuperior thigh the preceding night during a street fight using karate techniques. The patient had trouble walking because of pain. The medical history was significant for schizophrenia (type not specified) for which the patient was taking fluphenazine hydrochloride, 2.5 mg three times a day, and benztropine mesylate, 1 mg twice a day. The patient had had a right thumb pinning in the past at a nearby hospital. The patient admitted to drug, alcohol, and tobacco abuse and denied any allergies. The family history and a review of systems were noncontributory.

On physical examination, the patient was found to be afebrile with a heart rate of 78 beats/min; respirations, 20/min; and blood pressure, 110/70 mm Hg. There was direct tenderness in the right inguinal area and minimal discomfort with internal and external rotation of the right femur. There was pain with axial compression loading. The neurovascular response was within normal limits.

The laboratory evaluation was normal except for a lactate dehydrogenase level of 506 U/L and creatinine phosphokinase of 775 U/L. Urinalysis showed trace blood:

3-5 red blood cells. The white cell count was 11,400 with a normal differential. The hematocrit, hemoglobin count, and electrocardiogram were within normal limits. Radiographic evaluation of the pelvis showed acute fractures of the right acetabulum and the inferior portions of the right pubic ring (Fig 1, 2).

The patient was noted to have 50° of hip flexion with 20° of internal and external rotation. He was evaluated by an orthopedic consultant and was admitted to the hospital and placed in 5 lbs of Buck's traction. His condition improved, he was started on physical therapy, and on hospital day five he was discharged. The patient was instructed to not bear weight on the right lower extremity and was given 20 mg of piroxicam for pain. A repeat pelvic radiograph on five weeks after the original injury, showed a healing stable fracture through the floor of the right acetabulum.

DISCUSSION

The speed and force generated by common upper and lower body tech-

niques in the Martial Arts have been studied and recorded.^{5,9,11} The side kick has been shown to produce the most power under laboratory conditions and has caused at least one death.^{8,11} The force required to produce the injury reported here is unknown and depends on the focus, speed, and strength of the attack, as well as the positioning of the defender.

A five-year national survey on martial arts injuries found that 15% of such injuries were fractures and dislocations.³ The most common injuries were contusions, sprains, bruises, and strains.^{3,6} More serious injuries, such as viscus rupture, cerebral concussion, infarction, contusion, and death have also been recognized.^{4,1,2,8,7} Stricevic et al¹⁰ noted that punches accounted for a higher injury ratio than did kicks. Such injuries result from repetitive action, direct impact, or ballistic and torsional maneuvers. The case presented here demonstrates the serious consequences of lower body blows to bone structures. Coexistent soft tissues and hollow and/or solid organ injuries must always be considered.

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FIGURE 1. AP of pelvis showing fractures of the right acetabulum (black root) and the pubic ring (white arrow).



FIGURE 2. Right oblique of the pelvis demonstrating fractures of the right acetabulum (black arrow) and pubic ring (white arrow).

Constrictive pericarditis presenting as bilateral pleural effusions—a diagnostic challenge

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Although constrictive pericarditis is a recognized cause of pleural effusions, several reviews have failed to include it in the differential diagnosis of pleurisy, and often it is not considered as a cause of pleural disease.^{1,2} We report a case of idiopathic constrictive pericarditis in which there were no physical signs consistent with that diagnosis, except for the presence of bilateral pedal edema; in addition, the initial echocardiographic study was nondiagnostic.

CASE REPORT

A 55-year-old man presented in December 1988 with progressive dyspnea and a cough productive of white sputum. The physical examination was unremarkable except for dullness and decreased breath sounds at the lung bases and mild bilateral pedal edema. A chest radiograph revealed bilateral pleural effusions (Fig 1). An echocardiogram showed normal left ventricular function, a small pericardial effusion with normal ventricular septal motion, and a normal pericardium. The electrocardiogram revealed low voltage (Fig 2). A computed tomographic (CT) scan of the chest and abdomen confirmed the presence of bilateral pleural effusions with no other abnormalities reported. Laboratory tests for antinuclear antibody, rheumatoid factor, sedimentation rate, thyroid function, and liver function were all within normal limits. The patient was anergic to skin testing including a tuberculin test. The pleural fluid was consistent with an exudate with a total protein of 4.1 g/dL; lactate dehydrogenase level, 71 U/L; glucose, 111 mg/dL. The total number of red blood cells were 450/mm³, and the white blood cells totaled 258/mm³, 94% of which were mononuclear cells. Bilateral pleural biopsies showed normal pleura.

In view of a significant exposure to asbestos 40 years earlier, the possibility of mesothelioma was entertained, and the patient was referred to Memorial Sloan-Kettering Cancer Center for a thoracotomy.

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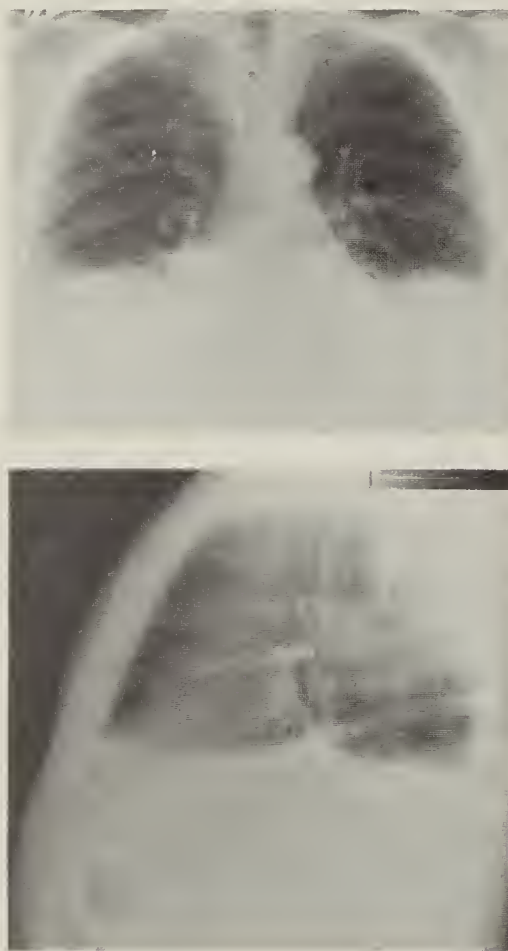


FIGURE 1. Left, posteroanterior chest roentgenogram showing bilateral pleural effusions. Right, lateral view.

During a right-sided thoracotomy, approximately 3,500 cc of straw-colored fluid with a fibrinous gel was removed. The pleura, lung, and mediastinum appeared grossly normal. The pathology report on the pleura revealed chronic inflammation with mesothelial hyperplasia and no evidence of malignancy. To rule out lymphoma and infectious granulomatous disease, a bone marrow aspirate and biopsy were performed, which were normal. Routine fungal and mycobacterial cultures showed no growth.

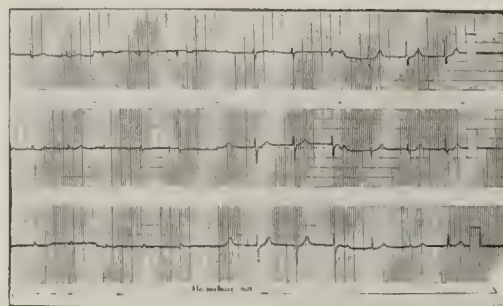


FIGURE 2. Electrocardiogram showing low voltage.

In May 1989, several months after the thoracotomy, the patient appeared to be improving with some regression of the effusions. However, the following month, he noted worsening of the pedal edema. On physical examination, no jugular venous distension, hepatojugular reflux, or Kussmaul's sign were noted. Cardiac examination revealed a soft systolic ejection murmur at the left lower sternal border without any gallops; moderate pedal edema was present. An echocardiogram showed a small pleural effusion and some pericardial thickening, which was not noted before the thoracotomy and was thought to have been caused by the surgery (Fig 3). Doppler wave forms at the time of this study were not suggestive of constrictive pericarditis.

The patient was referred to a cardiologist, and a cardiac catheterization was recommended to evaluate the patient for the possibility of constrictive pericarditis or a restrictive cardiomyopathy. Results of the catheterization revealed equalization of both right and left ventricular end diastolic pressures with a square root sign (Fig 4), consistent with the diagnosis of constrictive pericarditis. In an attempt to exclude a restrictive cardiomyopathy, an endomyocardial biopsy was done and was found to be normal. Pericardiectomy was subsequently performed. Pathologic review of the pericardium showed fibrosis. All cultures were negative for organisms including those for mycobacteria and fungi, and no definite etiology for the constrictive pericarditis was found.

DISCUSSION

Pleural effusions have been reported to occur in 50%–60% of patients presenting with constrictive pericarditis.^{3–5} The possibility of constrictive pericarditis is often not

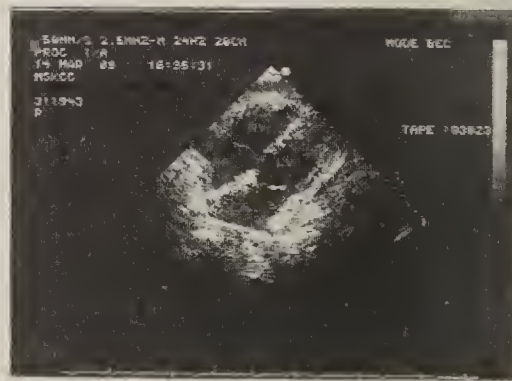


FIGURE 3. Echocardiogram: RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium; PT, pericardial thickening.

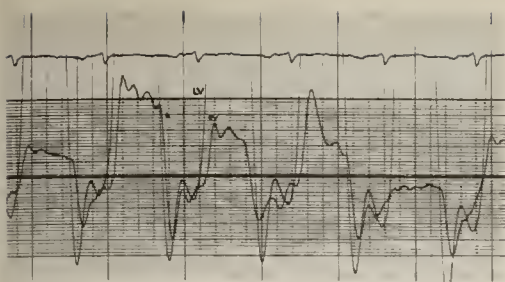


FIGURE 4. Tracing obtained during cardiac catheterization demonstrating the square root sign: LV, left ventricle; RV, right ventricle.

considered in the initial evaluation of pleural effusions, since the physical examination and noninvasive studies may not support the diagnosis. In occult constrictive pericarditis, the physical examination is usually normal, and a diagnosis is not made until cardiac catheterization is performed.^{6,7} Kilman et al⁷ reported on 12 patients with this syndrome; only one of the patients had peripheral edema, and another had a pleural effusion.

At times, however, the physical examination may be helpful. Jugular venous distension has been reported in 39%–95% of patients, Kussmaul's sign in 13%–27%, ascites in 28%–89%, a pericardial knock in 30%–58%, and pedal edema in 45%–68%, according to some reports.^{3,8,9} On echocardiogram, pericardial thickening, abnormal ventricular septal motion, and flattening of the posterior ventricular wall in diastole are suggestive of constrictive pericarditis. In Schiavone's⁹ article, these findings were reported in 95%, 84%, and 74% of the cases, respectively. The pitfalls of an echocardiogram, however, include the inability to detect early constriction and the variable quality of the echocardiographic picture.¹⁰

The only physical sign present in the patient described here was pedal edema. Initial cardiac evaluation, in-

cluding echocardiography, revealed a small pericardial effusion, which is a nonspecific finding, although it has been noted to occur in 3%–44% of patients with constrictive pericarditis.^{3,9}

Cardiac catheterization remains the definitive procedure used for the diagnosis of constrictive pericarditis. Findings consistent with the entity include a prominent y descent, the square root sign, and equalization of pressures during diastole.³ The y descent occurs during early diastole and represents a decrease in venous pressure wave form secondary to the relaxation of the ventricular myocardium. It reflects a period of unimpeded blood flow. As the ventricle rapidly fills during the restricted phase of diastole, a steep rise in ventricular pressure is seen. This is followed by a phase when little or no further filling of the ventricles occurs, referred to as the plateau pressure.¹¹ These findings may be further enhanced by giving a bolus of intravenous fluid (volume loading), which would raise filling pressures in non-compliant ventricles that are restricted by a rigid pericardium. This constriction leads to the equalization of pressures at the end of diastole in both ventricles. Volume loading is especially helpful in making a diagnosis of occult constrictive pericarditis, since tracings obtained during routine cardiac catheterization are often normal.⁷

The classic causes of constrictive pericarditis, such as tuberculous infection and purulent pericarditis, are now seen less often.⁹ Although postradiotherapy and postsurgical constriction continue to be important causes of constrictive pericarditis, the idiopathic form is the most common type.^{3,8} This patient had idiopathic constrictive pericarditis, which was the cause of the

bilateral pleural effusions. The development of pleural effusions in this patient was probably related to the associated hemodynamic abnormalities. It has been stated that venous drainage from the pleura may be impaired by elevations in left atrial pressure and associated pulmonary venous and capillary hypertension.³ Pleural lymphatic drainage is probably impaired as well due to elevated right atrial pressures.

We present this case to illustrate that the diagnosis of constrictive pericarditis can be elusive. Physical examination and echocardiography may not be helpful, and cardiac catheterization is often the only diagnostic procedure. Constrictive pericarditis should always be included as a possible cause of pleural effusion when no other cause is apparent.

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The human tail

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Only twenty-four cases have been reported in the medical literature in the past century.¹ We report an additional case in a child recently born at Central General Hospital in Plainview, NY. Of special interest is the fact that the parents of the child were never upset or anxious about the problem and were confident that modern medicine could remedy it. The medical and nursing staff, on the other hand, became concerned about issues such as the origin of man, teratology vs evolution, and Darwinism.

CASE REPORT

A male infant weighing 3,912 grams was born after a normal 40-week gestation. He appeared normal in all respects except for the presence of a sacral appendage. There was no history of maternal infection or exposure to known or suspected teratogens before or during the pregnancy. There was no family history of similar or related congenital anomalies.

The appendage measured 2.5 cm long, was 0.8 cm in diameter at its base, and was tapered at the tip (Fig 1). The growth was located 2 cm below the sacral dimple. It was covered by skin of normal texture and had a soft spongy consistency. No spontaneous movements of this appendage were noted. A neurologic examination was normal. Radiographs of the sacral area were normal and contained no bony structure.

When the infant was two months of age, the appendage was removed for cosmetic purposes (Fig 2). The pathologic description was "skin with adnexa and adipose tissue." The histologic findings were consistent with those reported by other investigators.²⁻⁶

DISCUSSION

In his definitive embryologic study, Harrison postulated that the human tail resulted from the persistence of the vestigial tail, usually the nonvertebral portion (caudal filament) of the 14-16 mm embryo.² Human embryos of 3 to 12 mm in length (from day 26 to day 40 postfertilization) have a segmented tail. The tail reaches its maximal length of 1 mm during the sixth week when the embryo is 12 mm long. With normal development, the embryonic tail undergoes regression because of physiologic cellular necrosis beginning in the dorsal chords. Normally, during the second month, the caudal primordium disappears entirely in man.

The development and disappearance of the human tail between stages 14 and 22 of development (days 32 to 54 postfertilization) have been studied using light microscopy as well as scanning and transmission electron microscopy. During embryologic stages 14 and 15 (days 32-35) the tail is a prominent feature of the developing human and is composed of somites, mesenchyme, and extensions of the neural tube, notochord, and gut. At stage 17 (day 41), the tail extends more than one millimeter from the trunk. Cell death and phagocytosis account for the disappearance of the tail.⁷

Tails and pseudotails are associated with other anomalies in 29% of cases,¹ with spina bifida being the most common. Other reported anomalies include meningocele, absent pedicles of the last two sacral vertebrae, club foot, cleft palate, small fourth toe, and lipoma⁸ at the base of the tail. In no case has a tail been found connected to the neuroaxis.¹

The frequency of this anomaly is not known, but it is extremely rare with only 24 true tails reported in the past century. The sex distribution among published cases is 11 females and 13 males.

Caudal appendages may include tails or other outgrowths or protrusions in the lower region of the back. Among these are lipomas, sacrococcygeal tumors, and pseudotails. Dao and Netsky⁵ define a true tail as a "caudal midline protrusion capable of spontaneous or reflex motion, consisting of skin covering a combination of muscle, adipose, and connective tissue, and normal blood vessels and nerves. In humans, a true tail is vestigial, however, and never contains vertebrae."⁵ The vestigial human tail is not related to the neurospinal axis. This differs from a "pseudotail," which is composed of other normal and abnormal tissues. These lesions are most often either prolongations of the coccygeal vertebrae, neoplasms, or myelomeningoceles.



FIGURE 1. Photograph of caudal appendage from a prone position.



FIGURE 2. Photograph after resection.

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We present another case of this rare human anomaly. We suggest that the diagnosis be made on clinical and radiologic grounds, that associated anomalies be sought out, and that resection be performed for cosmetic purposes.

Acknowledgments. The authors thank Ms Phyllis M. Warch for her editorial

assistance in the preparation of this manuscript.

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FROM THE LIBRARY

PROGRESS OF MEDICINE Test for Bilirubin

Obermayer and Popper of Vienna propose an improved modification of the reagent for the iodine test for bilirubin in the urine. The reagent consists of 625 ccm. water, 125 ccm. of 95 per cent. alcohol, 75 g. sodium chloride, 12 g. potassium iodide, and 3.5 ccm. of ten per cent. tincture of iodine. With a pipette a small quantity of this reagent is carefully overlaid on 5 ccm. of urine in a test tube. The urine should be fresh, of acid reaction, filtered, and if very dark diluted with physiologic salt solution. At the boundary line of the two liquids a green, bluish, or bluish-green ring is seen, corresponding in intensity with the amount of bilirubin present. By this test bilirubin is regularly found in small quantities in most normal urine. Aside from the diseases with icteric discoloration of the skin, a number of others show a pathologic increase of bilirubin, among which are muscular and valvular heart lesions with insufficiency, atrophic liver cirrhosis, croupous pneumonia, acute articular rheumatism, and certain pleural exudates. In pulmonary tuberculosis with high fever, on the other hand, it appears to be lacking—*Wiener klinische Wochenschrift*, 1908, No. 25.

HENRY L. ELSNER, MD
DE LANCEY ROCHESTER, MD
EDWARD H. SHEPARD, MD
(*NY State J Med* 1908;8:495-496)

Address correspondence to Editor, New York State Journal of Medicine, 420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to ensure prompt publication after editorial review. All letters are personally acknowledged by the Editor.

The physician and the poor

TO THE EDITOR: After reading Eli Ginzberg's editorial commentary, "The physician and the poor" in the June 1991 issue of the *Journal* in which he blames the medical profession for the spiraling high cost of health care without offering any true insights as to all of the possible sources, I read Thomas Weil's article in the same issue.^{1,2} I was even more dismayed with Ginzberg's comments, which failed to recognize the key points of Dr Weil's thesis.

Eli Ginzberg has been chastising the medical profession for years. As an economist, he continually advances the thesis that the United States has overproduced physicians. This excessive number of physicians has given rise to levels of utilization of therapeutic and diagnostic interventions, which are proving very costly to the American health care system.

It would behoove Eli Ginzberg to examine all of the economic factors which go into the health care equation and at least concede that a large proportion of the dollar goes into the inflated cost of drugs, supplies, and equipment. This is rather well known. In addition, the *New York Times* once again reported the figures for the national cost of the bureaucracy managing the health care system, which was alluded to in Dr Weil's article. Somewhere between 65 and 82 billion dollars a year are required for the paperwork involved in administering the myriad health plans.

Let me illustrate the point. Many of the surgical instruments that I use in my practice are grossly over priced. A \$2,900 cordless electric drill can be purchased at the hardware store for \$34.95. Although it may not be designated a "surgical instrument," it performs exactly the same function.

Similarly, we are all aware that the retail cost of drugs in the United States is many times greater than the cost of the same drugs manufactured by the same companies in Europe and Asia.

Of course in the United States, the constant threat of litigation fuels these inflated costs.

For these reasons, I applaud Dr Weil's article. Unless we recognize where the health care dollar is going, we will continue to shrink access to care and ration care which in the long run will do very little to stem the rising cost of health care.

Even to imply, as Dr Ginzberg does, that limiting the amount of money spent on research would have a beneficial long-term effect, further indicates a dangerously shallow approach to the health care problem.

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1. Ginzberg Eli: The physician and the poor. *NY State J Med* 1991; 91:236-237

2. Weil TP: Physicians and national health insurance: Some economic factors. *NY State J Med* 1991; 91:250-253

In reply: I read Dr Housepian's letter with consternation because I suddenly realized the scope for misinterpretation that the printed word permits. Were I to interpret Eli Ginzberg's past and current writing as Dr Housepian has, I would share his upset. However, I am unacquainted with the author he is tilting with. The United States health care system is sufficiently complicated without gross misreadings of the work of those of us who have spent their lives trying to understand and improve it.

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Joseph Isaac Bluestone, MD

TO THE EDITOR: I read with great interest and delight Dr Naomi Bluestone's wonderful piece about Joseph Isaac Bluestone, MD.¹ What a man, what a physician!

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1. Bluestone NR: The memoirs of Joseph Isaac Bluestone, MD. *NY State J Med* 1991; 91:254-261.

TO THE EDITOR: My compliments to Dr Naomi Bluestone on "The memoirs of Joseph Isaac Bluestone, MD," described in the June issue of the *Journal*.¹ The sections she selected make fascinating reading.

I was especially interested because my birth in 1911 was assisted by a doctor "J. Bluestone."

I have read Dr Bluestone's other writings in the *Journal* and have always found them interesting. Keep them coming.

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1. Bluestone NR: The memoirs of Joseph Isaac Bluestone, MD. *NY State J Med* 1991; 91:254-261.

TO THE EDITOR: Dr Naomi Bluestone's article on Joseph I. Bluestone was enjoyed.¹ There is always something to be learned from the past not the least of which is viewing ourselves in an historical context. Dr Bluestone's article makes that valuable contribution.

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1. Bluestone NR: The memoirs of Joseph Isaac Bluestone, MD. *NY State J Med* 1991; 91:254-261.

TO THE EDITOR: Thank you for publishing Dr Naomi Bluestone's arti-

cle about Joseph Isaac Bluestone, MD, in the June issue of the *Journal*.¹

I read the article three times, and each time became more grateful to Dr Bluestone for having introduced me to such a fine and delightful gentleman.

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1. Bluestone NR: The memoirs of Joseph Isaac Bluestone, MD. *NY State J Med* 1991; 91:254-261.

Symptomatic duodenal web in the elderly

TO THE EDITOR: Duodenal web accounts for 25% of all obstructive lesions of the intestinal tract in neonates.¹ The incidence of symptomatic duodenal web in the elderly population is not known. This report describes a woman who presented with gastric outlet obstruction secondary to duodenal web.

Case Report. A 72-year-old woman presented with a one month history of vague, epigastric pain which worsened at night. She also experienced nausea, which was relieved by self-induced vomiting. She denied dysphagia or weight loss. The past medical history included a right modified radical mastectomy for carcinoma and bilateral hip replacement for osteoarthritis. The only medication the patient took was occasional aspirin.

The physical examination revealed a well-nourished female appearing her stated age. The vital signs were within normal limits and the chest and cardiovascular examinations revealed no abnormalities. The abdomen was soft and nondistended, and no masses were palpable. The rectal examination was normal, and no jaundice was present.

Laboratory findings were normal as was an abdominal X-ray. An upper GI endoscopy suggested "an extrinsic compression on the second portion of the duodenum." An abdominal CT scan revealed a dilated stomach but no mass was seen in the pancreas.

Gastric distension was found at exploratory laparotomy and the duodenum was contracted and in spasm. No mass was palpable in the pancreas. Duodenotomy was performed and two webs, located proximal and distal to the Ampulla of Vater, were found. Palpation of the webs revealed almost complete obstruction of the lumen. The webs were lysed and the duodenum closed. No mucosal inflammation was seen in the duodenum. Gastrojejunostomy was then performed. Eight months after discharge, the patient was asymptomatic and doing well.

Discussion. The most common causes of congenital duodenum obstruction are atresia, annular pancreas, peritoneal band, and volvulus.² However, symptoms of the above usually occur during the neonatal period. Hudson³ reported a 37-year-old male who presented with vomiting and abdominal pain. On exploration, an occlusive diaphragm was found proximal to the Ampulla of Vater. Kreigh⁴ reviewed 21 patients and reported diaphragmatic web-type obstruction could be encountered throughout life. The youngest reported was a stillbirth, and the oldest was 70 years old. The site of the lesions were 45% proximal to the ampulla, 20% opposite to the ampulla, and 25% distal to the ampulla. Ten percent were located at the duodenojejunal junction.

The etiology of this condition is thought to be the incomplete vacuolization of the embryonic intestinal lumen or vascular insufficiency during the development of the intestine.¹ Ross et al⁵ postulated that the late presentation of symptoms might be the result of unrecognized inflammatory episodes occurring during adult life. This would give rise to further narrowing of the aperture. Surgical treatment of this disease involves excision of the web and the closure of the duodenotomy. Gastrojejunostomy is indicated if significant compromise of the duodenal lumen occurs while performing the above procedures.

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Imaging of parietal thinning

TO THE EDITOR: Parietal thinning is an asymptomatic condition which is observed incidentally in some elderly patients when they are examined



FIGURE 1. Lateral plain film of the skull shows thinning of the parietal bone (arrows).

radiographically because of cerebrovascular accidents or head trauma. Traditionally, plain films have demonstrated increased lucency in the parietal regions of the skull. However, it was not until the advent of computed tomography (CT) and the generation of axial images of the calvarium that the significance of the parietal lucency seen on plain films was fully appreciated. We present a case of parietal thinning that was evaluated with various imaging modalities including plain films, CT, and nuclear scintigraphy.

Case Report. A 87-year-old man with known Pagets disease presented with a progressive two year history of dementia. He was admitted to the hospital on multiple occasions for recurring syncopal episodes and head trauma. He was also noted to have a recent onset of atrial fibrillation. Earlier medical history showed that the patient had a transurethral prostatectomy performed 15 years before this current admission for benign prostatic disease. Plain films of the skull showed no evidence of fracture. However, there was evidence of increased lucency bilaterally in the parietal bones. (Fig 1) CT showed a moderate degree of cortical atrophy and an area of decreased attenuation within the right basal ganglion compatible with an old infarct. Bone windows demonstrated symmetrical thinness of the parietal bones bilaterally. A subsequent nuclear bone scan using 25 mCi of ^{99m}Tc MDP showed no evidence of decreased or increased uptake in the calvarium, particularly within the parietal regions. (Fig 2)

Discussion. Parietal thinning has been known to occur since the 18th century. This entity was described in Egyptian mummies and also in a female cranium from Harappa, India,



FIGURE 2. ^{99m}Tc MDP bone scan shows no definite defects in the parietal regions.

belonging to the Bronze age culture dated to 2300 BC.¹ The etiology of this often incidentally found condition is not known, but many theories have been put forth. Steinbach et al² presented cases that showed that this entity may be acquired and that progressive disease may develop over several years. They showed that in one case, followed over a period of 16 years, that there was a disappearance of the diploe and a depression in the outer table of the skull, which retained its normal thickness. In the region of maximum involvement, the diploe disappeared completely. They also related the thinning of bone to osteoporosis, since this condition was presented in many of the case reports they reviewed. Schmidt indicated that there was a lack of osteoblasts with diminished bone formation rather than increased bone destruction.³ This again supports the notion of an etiology of osteoporosis.

In a review of 119 patients, Camp and Nash⁴ observed that the majority of their patients were male and that ten patients of the total group were under 30 years of age. They therefore concluded that since some of their patients were too young to have senile or post-menopausal osteoporosis, that the lesion must be related to diploic dysplasia. However, Steinbach² explained that thinning localized to the parietal bones may be due to decreased osteoblastic activity as a result of gonadal insufficiency, senility, or some other cause of osteoporosis in a region of minimal stress or strain. Bruyn and Bot⁵ showed that this condition is not common and estimated that there is a prevalence rate of .25%–.8%. Cederlund et al⁶ reported a prevalence of 2.3% when they included cases they thought might be overlooked if not specifically sought after.

Although this condition occurs sporadically, a familial relationship has been reported⁵ and occurs more frequently in women than in men. Why this entity is more common in woman is not certain. Most cases are seen in older age groups, in men who are 50 years of age or older, and in women who are above 60 years.

The plain film findings of increased lucency in the parietal regions are quite characteristic and are now supported by axial CT demonstration.

Thinning may be symmetrical or asymmetrical and primarily involve the outer table of the diploic space in a saucerized manner producing beveled edges.

In our case, the ^{99m}Tc MDP bone scan showed homogenous uptake in the calvarium, and no suggestion of decreased metabolic activity in the parietal regions. No bone defects were appreciated in the parietal regions, but this may have been due to a superimposition of structures. Parietal thinning by itself appears to be of no clinical significance, except that patients with this condition are at increased risk for skull fractures and intracranial hemorrhage even with insignificant head trauma.

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BOOK REVIEWS

COLOR ATLAS OF OPHTHALMIC PARASITOLOGY.

By B.H. Kean, MD; Tsieh Sun, MD; Robert M. Ellsworth, MD. 233 pp, illustrated. Igaku-Shoin Medical Publishers, Inc, 1991. \$110.00 (hardcover)

Three eminently qualified authors have collaborated to fill a literature gap with a 233-page atlas and text on some 30 parasitic diseases which affect the human eye. This is not an exhaustive treatise, but rather a thorough coverage of each clinically important disorder. It is aimed at the ophthalmologist more than the parasitologist, although each should profit by the availability of this material. Introductory pages include sufficient basics to enable the non-ophthalmologist to achieve a good understanding of the ocular manifestations of each entity. There is also an ophthalmic glossary and a key to abbreviations used in the text.

The material is divided into five main parts: (1) diseases caused by protozoa, (2) by nematodes, (3) by cestodes, (4) by trematodes, and (5) by arthropods. The text is consistently referenced with recent publications, and it is accurately indexed.

The authors use the following sequence for each disease: epidemiology, parasitology, clinical features, pathology, laboratory diagnosis, treatment, references, and finally a collection of color or black and white illustrations of the clinical, laboratory, and pathological aspects.

Most parasitic diseases that affect the eye occur in tropical countries, but several (such as toxoplasmosis, toxocariasis, acanthamebiasis, and pneumocystis) are important entities with which every American ophthalmologist should be familiar. As the world "grows smaller" through transportation improvements and immigrations, it behooves us to know much more about parasitic diseases that seriously affect millions of persons in other countries.

If you are a reader who is accustomed to link diseases of the developing nations with public health issues, preventive medicine and socioeconomic concerns, you will find little of such material in these tersely written pages. The illustrations are quite ade-

quate, but not extraordinary in quality or quantity. However, for the western ophthalmologist, there is no other source material as complete or as current in its coverage of ocular parasitology. For the western parasitologist, there is no better laboratory reference book to aid in matching an identified organism with a specific disease entity. For many others with an interest in parasites and the eye diseases they may cause, this is the most definitive text they will require.

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MCDONALD'S BLOOD FLOW IN ARTERIES: THEORETICAL, EXPERIMENTAL AND CLINICAL PRINCIPLES

Third Edition. Edited by Wilmer W. Nichols, PhD, and Michael F. O'Rourke, MD. 456 pp, illustrated. Malvern, Pa, Lea & Febiger, 1990. \$98.50 (hardcover)

This, the third edition of *McDonald's Blood Flow in Arteries*, represents an exhaustive compendium of descriptive material that deals with the nature of flow of a fluid, the manner in which flow is affected by a number of recognized factors, and finally, a discussion of the implications of this material on aging, high blood pressure, and disease in humans, as well as therapeutic interventions. Portions are highly technical and can be appreciated only by those having had advanced instruction in mathematics and engineering. Most of the book, however, uses non-mathematical descriptive terms, so that it should prove of interest and value to those interested in blood flow and vascular diseases at any one of a number of levels of expertise.

The work is divided into 17 chapters. It starts with an historical review, proceeds to a general description of the nature of flow, and then turns its attention to turbulent flow and its relation to cardiovascular pathophysiology. Thereafter, the properties of the arterial wall are discussed, followed by a number of chapters on the detailed examination of pulsatile pres-

sure flow relations, measuring principles of arterial waves, the use of Doppler ultrasound devices and the contours of pressure and flow waves in different portions of the circulation. This includes discussions of the coronary and pulmonary circuits, as well. Vascular impedance and finally the therapeutic interventions as they relate to the characteristics of blood flow are described.

The original volume was the work of Dr McDonald, essentially writing alone, whereas the present edition is co-edited by Drs Nicholas and O'Rourke with chapter contributions by seven additional authors.

Some of the material initially seems overwhelming to a clinician with a basic interest in blood flow and reaction of the arterial wall to flow, but on further review there is much that can be recommended even to one with rudimentary training in mathematics and engineering. The reviewer plans to spend many hours in the coming years absorbing as completely as possible its voluminous contents.

For those interested in the subject of blood flow and arteries, it is recommended that a perusal of the contents of this work precede its acquisition. It is far too valuable an opus to be relegated to the dusty recesses of one's library because of the somewhat daunting appearance of the mathematical engineering formulae.

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GENERAL SURGERY: CURRENT STATUS AND FUTURE TRENDS

Edited by T.E. Starzl, W. Montorsi. 502 pp. New York, Raven Press, 1989. \$105.00 (hardcover)

This text represents a compilation of lectures delivered at the XXVI World Congress of the International College of Surgeons. The intent of this manual is to provide surgeons with a state of the art surgical book. The book attempts to cover a wide field of material from ophthalmology to otolaryngology, endocrine surgery, thoracic surgery, and traumatology, to name

but a few. No order or logical thread could be discerned throughout the manual since all topics are mixed in sequence, as they were apparently recorded during the meetings.

The quality of the text is extremely variable ranging from a very sketchy outline to a comprehensive review of a topic. Furthermore, the layout is of poor quality, most of the material being a reproduction of a computer printout.

Overall, this book is confusing, of mediocre quality and falls short of its intent to inform the surgical community of advances in surgery. In addition, the buy cost is out of the range for similar publications in the field.

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ATLAS OF HERNIA SURGERY

Edited by George E. Wantz, MD. 240 pp, illustrated. New York, Raven Press, 1991. \$115.00 (hardcover)

The author's purpose is "to teach the surgery of hernia of the abdominal wall the way it's taught in the operating room: by visual demonstrations with instructions." Dr Wantz worries about the "Perpetuation of antiquated or wanting procedures by surgeons who may be vague about newer concepts and techniques." In the forward by Dr Wantz's close colleague, Rene E. Stoppa, MD, a claim for instructional authority is made because he includes only procedures that through his personal experience (over 7,000 cases) he knows to be most effective. However, as Dr Stoppa also mentions, "hernias of the abdominal wall are diverse lesions matched only by the diversity of methods of treatment." With only a single author's experience, Wantz risks the same error he seeks to avoid and that he ascribes to learning hernia surgery in the operating room.

The book has 12 chapters, including chapters on anatomy, etiology, anesthesia and parastomal hernias, and the usual abdominal hernias. Each begins with a brief narrative including history and indications. This is followed by technique(s) with drawings. The drawings are purposefully designed to be simple and concise. They are in black and white and contain no labels, rendering them confusing at times. Each chapter ends with a bibliogra-

phy. This book is easy reading and generally flows smoothly.

The chapter on anatomy is somewhat vague, with a superficial discussion of the anatomy of femoral hernias. Wantz bases his philosophy of hernia repair on the myopectineal orifice concept advanced by Fruchaud. The chapter on etiology is a brief and interesting summary of this concept. The anesthesia chapter illustrates only local anesthesia which is strongly advocated by Wantz. A long chapter, "Classical anterior hernioplasty," opines that only three of the classic hernioplasties have stood the test of time: the Marcy simple ring closure, the Bassini operation (which includes the Shouldice clinic modification), and the McVay-Lotheissen-Cooper ligament repair. He acknowledges that all show excellent results when performed expertly in the appropriate patients. Wantz describes these procedures in three parts, dissection, repair, and closure. He declares that the dissection and closure are essentially equal in each procedure, with only repair differing. The section on dissection is strong and useful for any junior resident just learning hernia repairs. The use of prosthetic material in the repair of inguinal and femoral hernias is a well written section from a conceptual viewpoint. However, the illustrations and text describing the prosthetic repair of giant ventral hernias using a series of clamps to place the prosthesis is confusing.

Repair of femoral hernias does not include repair from below. The author states his fear of using a prosthetic repair at times because of infection. Yet, the only repair for parastomal hernias he illustrates is with prosthetic material.

Overall, in spite of the limitations that an atlas has from a single author, the author has met his stated objective. The resident reviewer of this book found it useful. The senior attending reviewer found little to recommend the book for individual purchase, but would consider it as an addition to the library. This atlas will not supplant the more encyclopedia hernia monographs currently available.

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THE AIDS DISASTER: THE FAILURE OF ORGANIZATIONS IN NEW YORK AND THE NATION

Edited by Charles Perrow, Mauro F. Guillen, PhD. 206 pp. New Haven, Ct, Yale University Press, 1990. \$25.00 (clothcover), \$9.95 (paperback)

In this book, the authors attempt to detail the organizational failures that led to the lack of an appropriate response to the epidemic of HIV disease that appeared in the early 1980s. They do not confine their analysis to governmental organizations. Rather, they also attempt to review both private funding agencies as well entities such as the blood industry.

The senior author, Charles Perrow, is a sociologist and Professor in the Department of Sociology at Yale. Mauro Guillen was a PhD candidate in sociology at the time the book was written. As the senior author states in the acknowledgements, he had not worked in the health field for 20 years. The questions they attempted to pose in developing this book was whether organizational theory could contribute to the understanding of the dynamics of the AIDS epidemic.

The content of the book is based on a series of interviews, and more significantly, on published material. It was clear that Randy Shilts' popular book on the AIDS epidemic, *And the Band Played On*, was important in directing this book.

The book is organized in a series of eight chapters that initially examine the early knowledge of the depth of the crisis and the failure of multiple organizations to address its development. It then proceeds to examine AIDS within the larger context of the prevailing environment of the Reagan years and to examine specific organizational responses.

This book ultimately fails in its major goal. Although its description of the early years of the epidemic is helpful, it founders in its major task. First, it attempts to deal with far too many types of organizations (from the blood industry to community service organizations), a task that is not compatible with a 200 page book. Second, it makes little or no attempt to dispassionately deal with organizational failures. Rather than extending their theories of organizational dynamics, they deal with issues of personality and occasionally innuendo. Finally,

large portions of the book are devoted to organizations that are not in New York, thereby diffusing the message.

There will someday be a textbook that clearly defines the organizational failure of New York's public and private sector to respond to the AIDS epidemic. This book does not accomplish that goal.

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AIDS CLINICAL REVIEW 1990

Edited by Paul Volberding and Mark A. Jacobson. 280 pp, illustrated. New York, Marcel Dekker, Inc, 1990. \$89.75 (hardcover)

In the past, practitioners interested in the care of the HIV-infected patient could glean the entire medical literature and collect almost every publication and newspaper clipping concerning the subject. With specialized journals, newsletters, texts, and a multitude of original contributions, a review of the most pressing issues by experienced clinicians and investigators is most welcome.

The book is edited by Dr Paul Volberding, internationally recognized in the field of HIV care, now Associate Professor of Medicine in Residence at the University of California, San Francisco, Chief of the Medical Oncology Division and Director of the AIDS Activities Division of San Francisco General Hospital; and Dr Mark Jacobson, Assistant Professor of Medicine in Residence, Divisions of Infectious Diseases and Clinical Pharmacology, at the University of California, San Francisco, and the San Francisco General Hospital. Dr Jacobson co-chairs the NIAID AIDS Clinical Trials Group, Cytomegalovirus Pathogen Study Group. The intention of these editors was to deliver a volume that examined critically selected topics in timely manner. Consequently, all thirteen chapters were written within nine months of publication. The contributors are both bicoastal and well qualified. Two medical students made valuable contributions.

An ominous choice of 13 topics includes occupational transmission and the ethics of physician risk and respon-

sibility; epidemiology; race, gender and sexuality; predictors of disease progression; oral lesions; HIV-related thrombocytopenia; Kaposi's sarcoma; diagnosis of *Pneumocystis carinii* pneumonia; ganciclovir therapy for cytomegalovirus disease; disseminated *Mycobacterium avium* complex disease; cryptococcal disease; toxoplasmic encephalitis; and anti-retroviral therapy. All chapters read as expertly delivered grand rounds, adequately illustrated with charts and diagrams. All topics are referenced with from ten to over 200 citations, some as late as 1990. There are three clinical photographs, all of oral lesions and all in black and white. These photographs demonstrate the pathology involved and are professionally reproduced in the text.

Because of the high quality of both writing and expertise, the reader is left wanting more. The chapter on physician risk and responsibility is unfortunately the shortest, but the editors have chosen this piece as their lead. Chapter three ("Race/Gender Issues in the Sexual Transmission of AIDS") will make the clinician aware of the complexities involved in planning effective education and preventive campaigns. This short, but most thoroughly referenced chapter (207 citations) discusses methodology, work related to attitudes on birth control, and the disturbing fact that significant racial differences exist concerning the issue of "safe sex" and condom use. Although the three paragraphs on the relationship between drug use and the spread of the HIV are brief, they do point out the phenomena of directly bartering sex for drugs in the crack culture.

The discussion of oral lesions of HIV infection discussed Kaposi's sarcoma, AIDS-associated lymphoma, periodontal disease, *Herpesviridae* infection, thrush, salivary gland disease, and oral ulcers. Our experience differs somewhat from these authors' experience concerning oral candidiasis. We found that topical preparations often fail. We have most recently substituted low-dose oral fluconazole for ketoconazole and have not had difficulty with elevation of liver function studies. Most illuminating was the section on the clinical presentations and treatment of periodontal disease in the HIV-infected patient.

The discussion of the pathogenesis and review of treatment strategies for HIV-related immune thrombocytopenia is erudite with complete and very

practical references. Dr Jacobson contributed the section on ganciclovir therapy for cytomegalovirus disease. Although complete, well written, and informative, it would have been helpful if additional data on foscarnet were presented. Drs Bozzette and Waskin's article on cryptococcal disease in AIDS reminds us of the frequency of eye and prostate involvement in addition to very complete discussions on diagnosis and acute and maintenance treatment regimens. The concluding chapter on antiretroviral therapy describes retroviral replication, mechanisms of action, and results of in vitro testing and limited in vivo trials of combination therapy. The authors do not discuss vaccine development.

In summary, *AIDS Clinical Review 1990* represents an authoritative, well-written update and interpretation of the complex HIV literature. The rapidity of publication and timeliness of the information makes this book unique and is a credit to the authors, editors, and publishers. I recommend this text for all practitioners in the field of HIV care, although the price is prohibitive. We should all be looking forward to the next and hopefully expanded edition.

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ONCOGENES

Volume I and II. Edited by Enrique Pimental, MD (ed). Boca Raton, Florida, CRC Press, 1989, Volume I, 528 pp, \$195.00 (hardcover); Volume II, 448 pp, \$195.00 (hardcover)

This book is so wide in a scope that it contains all essential clinical and research work that has been done on oncogenes, up to 1989. It serves both the clinical and basic science investigator.

While lately books of such a wide scope are finally written by an editor and several co-authors, the tremendous task of reviewing oncogenes has been accomplished here by just one individual. From the various subjects it appears that Pimentel is very well informed about carcinogenesis and oncogenes, covering the field thoroughly and lucidly. Furthermore, the author's approach is both scholarly

and critical. Among the literature cited are some essential publications in French, German, and Spanish. For example, the historical publication in 1928 about the mutation theory of carcinogenesis by Bauer is in German. The Spanish language publications represent some of the work that the author has done himself.

The text is organized so that one not having knowledge about a particular subject can obtain complete information. For example, from the text and the reference about mouse mammary tumor virus, one can get detailed information about its structure, function, and its relationship to human breast carcinoma.

In Vol. I there are six chapters: "General Biological Aspects of Oncogenesis," "Acute Retroviruses," "Chronic Retroviruses," "Endogenous Proviruses," "DNA Viruses," and "Viral and Cellular Oncogenes." In Vol. II, there are three chapters: "Function of Oncogene and Protooncogene Protein Products," "The Rous Sarcoma Virus Oncogene and its Protooncogene Counterpart," and "Protooncogenes and Cancer." At the end of each volume, there is a list of abbreviations commonly used in oncology and molecular biology, which facilitate an understanding of the text.

In Chapter 1, the author discusses basic concepts in oncogenes, hypotheses, and the various modalities of transformation from the normal to malignant cells. There is a clear definition and characterization of malignant cells. In Chapter 2, the general characteristics of acute retrovirus are reviewed with a list of 24 oncogenes and corresponding acute transforming retrovirus strains and the species from which these viruses were isolated. There are outlines of the processes leading to transformation by the viral oncogene proteins, the requirements for exogenous growth factors, and autocrine stimulation. These retroviruses are capable of inducing transformation in vitro as well as in susceptible animals. Chapter 3 describes the structure of the chronic retroviruses (slow viruses). Besides transformation, these viruses induce other diseases, among them AIDS. The endogenous proviruses are reviewed in Chapter 4. Evidence is presented that these sequences are present in the human genome, are inherited, and can be expressed as RNA and proteins. DNA viruses are reviewed in Chapter 5. Some of the viruses like the Epstein-

Barr virus may possess oncogenic potential. Historical development of the oncogene concept and definition of protooncogenes are discussed in Chapter 6. It includes evolution, chromosome localization, and expression of protooncogenes, as well as structure, detection, and characterization of oncogenes.

Chapter 7 contains a discussion of the function of oncogene and protooncogene protein products. The protein products of the following oncogenes are described in detail: *sis*, *erbB*, *neu/erbB2*, *erbA*, *ras*, *abl*, *fes/fps*, *fgr*, *fos*, *myc*, *myb*, *mos*, *fms*, *mil*, *mht/raf*, *rel*, *ros*, *yes*, *kit*, *crk*, *ets*, *erg*, *jun*, and *met*. There is also a description of putative protooncogenes, particularly those from the *src* family. There is an outline of the p53 gene and the function of its protein. Chapter eight is entirely devoted to Rous sarcoma virus oncogene and its protooncogene counterpart. The final chapter, Chapter 9, contains 1,297 references. In a very concise manner, the author discusses the relationship among protooncogenes and cancer. Oncogenically active protooncogenes in tumor cells such as *c-ras*, *c-lym*, and *c-raf* are reviewed. There is a discussion of the activation of other genes. Significant factors in carcinogenesis are the altered expression of protooncogenes such as *c-ras*, *c-myc*, *c-src*, *c-erbB*, *c-neu/erbB2* as well as amplification, mutation, translocation or rearrangement of protooncogenes especially in lymphomas and leukemias. This discussion is followed by a very detailed presentation of the mechanisms for the increased transforming potential of mutant p21^{c-ras} proteins. Among carcinogenetic factors, gene deletion or inactivation in such tumors as Wilms tumor, rhabdomyosarcoma, retinoblastoma, osteosarcoma, meningioma, lung carcinoma, colon carcinoma, leukemia, and multiple endocrine neoplasia is mentioned.

In conclusion, the author indicates from his present evidence that oncogenes, protooncogenes, and tumor suppressor genes contribute with other factors to multistage carcinogenesis. Even though these protooncogene studies have not made a major impact on the practical aspects of clinical diagnosis, prognosis, and treatment, they have substantially increased our understanding of the complexity of carcinogenesis.

There is no other book that covers this subject so thoroughly and that can

compete with it. Clinical and basic science investigators in oncology will find it very useful.

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MAYO CLINIC FAMILY HEALTH BOOK.

By the Mayo Clinic. 1,396 pp, illustrated. New York, William Morrow & Co, Inc, 1990. \$34.95 (hardcover)

Doing medical writing for the lay public is never easy, yet approximately 200 Mayo clinic contributors to this mammoth work have succeeded in doing just that. The purpose of this book is to inform lay persons how best to care for themselves in health and disease.

The book is organized into five parts. The first one takes the reader through the human life cycle from newborn, through pregnancy, to old age, describing the developmental changes and tasks faced at each phase. The second begins with a chapter on first aid and emergency care that goes on to discuss safety and to provide health information for travelers. Part three explores preventive strategies including exercise, nutrition, dental care, controlling stress, and the avoidance of substance abuse. More than half the book is devoted to part four, which gives specific patient information on nearly 1,000 ailments including dental problems. Each disease is covered in a standard format: signs and symptoms, basic description of the disease, how the physician makes the diagnosis, the prognosis, and treatment. Part five describes the US health care system; there are also chapters on medications, cancer, home care, death and dying.

In addition, both the atlas of human anatomy and the photographic guide to common dermatologic problems are in color. Appendices include a drug directory, a chapter on diagnostic tests, and a glossary of medical terms. The book is well indexed and has over 500 illustrations.

This work is edited by David Larson, MD, Associate Professor of Internal Medicine at the Mayo Medical School. Dr Larson is a board certified gastroenterologist who is well published in his field. He succeeds in his goal of producing a comprehensive

medical guide for direct use by the public.

He may have had difficulty editing the work of so many other contributors, and this is evidenced by a fair amount of repetition in the book. For example, identical drawings that illustrate how to take an infant's temperature appear no less than three times in the text.

However, the book is written in clear and simple language. The authors are careful not to frighten lay readers about their symptoms or attempt to usurp the role of the physician by teaching patients to perform independent self-diagnosis. In recognition of the fact that many aspects of medicine are controversial, they leave the options open enough so patients are aware that there is often no single right way to evaluate and treat disease.

Although the information is accurate, one minor mistake with an illustration is particularly glaring. The lumbar puncture figure shows the needle is inserted at the level of the spinal cord rather than inferior to it. This might add to widespread public fear of lumbar punctures and spinal anesthesia.

Technically, the book is well laid out. The thick blue lines that separate the different sections of each chapter tend to brighten the text, and the relatively large typeface makes for easy reading.

This book has the edge over the two others in its class. *The Columbia University College of Physicians and Surgeons Complete Home Medical Guide* (Genell J. Subak-Sharpe, ed.), Crown Publishers, 1989 (\$39.95) is

more expensive but less comprehensive. *The American Medical Association Family Medical Guide* (Jeffrey Kunz, MD, and Asher Finkel, MD, eds.), Random House, 1987 (\$29.95) is approximately two thirds the length of the Mayo book because of much less focus on preventive strategies and normal growth and development.

This book adds to the literature in being probably the most comprehensive medical reference available to the lay public. It is superior because of its strong focus on health issues and because it provides in-depth coverage of disease.

An important omission is a list of the names, addresses, and phone numbers of health organizations and resources. A separate chapter on human immunodeficiency virus (HIV) disease might also have been helpful. Incidentally, both chapters can be found in the Columbia book mentioned above. Nevertheless, this book is good value for the price and an excellent home medical reference. I feel confident recommending it to my patients and to the lay public at large.

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**MEDICAL ODYSSEYS. THE DIFFERENT
AND SOMETIMES UNEXPECTED
PATHWAYS TO TWENTIETH-CENTURY
MEDICAL DISCOVERIES**

By Allen B. Weiss, MD. 250 pp. New Brunswick, NJ, Rutgers University Press, 1991. \$36.00 (hardcover) \$13.95 (softcover)

This book is well written and easy to read. The author creates interesting and informative short stories about some of the most important medical discoveries that occurred during the 20th century. They range from the use of the "poison" mercury as a diuretic to the Chinese restaurant syndrome. Between them, he describes the diseases associated with a yellow skin, the discovery of penicillin, the use of artificial organs, the classification and treatment of heart defects, the naming and cure of pernicious anemia, the use of mustard gas, the poliomyelitis saga, and the Philadelphia plague, Legionnaire's Disease.

Each vignette provides the reader with interesting reminders as well as little known facts. As always, hard work, good fortune, and the prepared mind helped outstanding investigators to grasp and use the available information to achieve success.

I recommend this book to the laity interested in science, medical students, and practitioners. The latter will find it to be useful recreational reading. It will appeal to physicians in my age group who lived and practiced during the time so pleasantly described by the author.

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Egg-borne salmonellosis is a growing public health problem

Epidemiologic assessment of the *Salmonella enteritidis* infection epidemic has linked the disease in humans to consumption of infected eggs. Foods that include raw, unpasteurized, or lightly cooked eggs, in which the yolk remains in a liquid state, are potential carriers of *S enteritidis*. Hollandaise and bernaise sauces, Caesar dressing, and soft-boiled and sunny-side eggs are examples of foods to avoid.

Mishu et al demonstrated "a direct link between *S enteritidis* infection on a poultry farm and an outbreak of human disease" associated with intact, grade-A shell eggs (*Ann Intern Med* 1991; 115:190-194). Eighty-one persons in Tennessee reported symptoms of gastroenteritis—all had eaten dinner at the same restaurant on the same evening. Ninety percent of this group had consumed either hollandaise or bernaise sauce; none of the ten control subjects (non-ill dining companions) ate these foods. Of the stool cultures performed on 24 of the ill subjects, all grew *S enteritidis*. Nearly half of the patients required a hospital stay. "The median incubation period was 25 hours. The median duration of illness was 5 days."

The eggs used to make the sauces were traced to a farm in Indiana, which supplies eggs to another farm, described as "one of the largest egg suppliers in the United States." Cultures of the intestinal contents of some of the chickens and of eggbelt swabs grew *S enteritidis*.

The authors note that although only about 1 of 10,000 eggs is contaminated with *S enteritidis*, if the epidemic of infections continues to grow, eggs, like milk, may require pasteurization.

Ipsilateral breast tumor recurrence after lumpectomy is strong predictor of distant metastases

Previous studies have shown that in patients with breast tumors of 4 cm or less, treatment by either radical mastectomy, lumpectomy, or lumpectomy with breast irradiation does not yield a significant difference in survival or frequency of metastatic disease between the three treatment groups. However, nine years after this initial treatment, there was a notable difference in ipsilateral breast tumor recurrence (IBTR), occurring in 43% of lumpectomy cases, and 12% of women treated with lumpectomy and breast irradiation. Taken together, these findings suggest that IBTR does not appear to cause distant disease.

Fisher et al, however, were able to demonstrate that IBTR is "a highly significant independent predictor of distant metastatic disease" and could signal the need for systemic anti-cancer therapy (*Lancet* 1991; 338:327-331). "When an patient who has had a lumpectomy is diagnosed with an IBTR, her risk of distant disease increases, and the earlier the appearance of the IBTR,

the shorter the time to distant disease is apt to be," the investigators conclude.

Surgical versus medical treatment for otitis media with effusion

Ventilation tube (VT) surgery has become a relatively common pediatric procedure for treating otitis media with effusion (OME). OME, which is thought to be a sequela of acute otitis media, is the most common cause of hearing loss in children. Prompt and effective treatment for OME is essential in preventing hearing loss. Bernard et al suggest that a six-month trial of antimicrobial therapy might preclude the need for surgical intervention in a substantial number of patients (*Pediatrics* 1991; 88:215-222).

One hundred twenty-five patients with middle ear effusion and hearing loss of at least three months duration were randomly assigned to one of two treatment groups: medical—75 mg/kg sulfisoxazole, a sulfonamide-based antibacterial, given in two doses/day for six months; surgical—bilateral myringotomy and VT insertion. Patient evaluations, including audiometry and otomicroscopic examination, were performed at 2, 4, 6, 12, and 18 months after initiation of the study.

The investigators found that, for at least the 18-month period included in this study, although surgical management had a greater success rate than medical treatment, "33% of subjects with indications for VT surgery treated with sulfisoxazole for six months required no further intervention by 18 months after entry into the study." Considering the risks of anesthesia, the finding that significantly ($p < .001$) more surgical patients than medical patients experienced side effects of their treatment, and a cost comparison of the two treatment protocols, the investigators recommend that six months of antimicrobial therapy precede VT surgery. A second course of antimicrobial therapy, or therapeutic followed by prophylactic dosages of antimicrobials might further preclude the need for surgical intervention. In this study, 67% of medical patients and 48% of surgical patients required retreatment by VT surgery by the 18-month follow-up.

New drug is effective against migraine and cluster headaches

Sumatriptan, a selective agonist of 5-hydroxytryptamine (serotonin)-like receptors, appears to block the mechanisms that precipitate migraine and cluster headaches (*N Engl J Med* 1991; 325:316-326). The Subcutaneous Sumatriptan International Study Group randomly divided patients with active migraine headaches into three treatment groups: (a) placebo; (b) 6 mg sumatriptan; (c) 8 mg sumatriptan, all administered as subcutaneous injections. After 60 minutes, if the patients still reported any pain, groups (a) and (c) received an injection of placebo, whereas group (b) subjects received either placebo or a second injection of sumatriptan.

After the first 60-minute period, significantly more patients in groups (b) and (c) reported reduced severity of headache or complete resolution of pain, than for group (a) patients. There was no significant difference between the number of patients with improvement in groups (b) and (c). After 120 minutes, there was no significant difference in improvement of headache between the group (b) patients who had received either a second injection of placebo or an additional 6 mg of sumatriptan.

Sumatriptan was equally effective in patients who did

and did not have auras preceding their headaches. Symptoms such as nausea, vomiting, photophobia, and phonophobia responded significantly better to sumatriptan than to placebo. Of interest, the investigators of the study reported that "patients treated early (within the first four hours after the onset of symptoms) and those treated later responded equally well to sumatriptan."

In a related study, the investigators found that "sumatriptan was significantly more effective than placebo in reducing the severity of [cluster] headache . . . within 15 minutes of the injection ($p < 0.001$)."

FROM THE LIBRARY

THE RELATION OF MIGRAINE TO EPILEPSY

Headaches have been variously classified by different authors, and for many years migraine or megrim has been recognized as a distinct form. Liveing was one of the first to give a systematic description of the disease; and he is still referred to as authoritative. Gowers defines migraine as "an affection characterized by paroxysmal nervous disturbance of which headache is the most common element. The pain is seldom absent and may exist alone, but it is commonly accompanied by nausea and vomiting, and is often preceded by some sensory disturbance, especially by some disorder of sight." The symptoms often being one-sided, including especially the pain in the head, this disease has been called hemicrania, furnishing the French term migraine, and the English megrim. Charcot distinguished the disease as "ophthalmic" migraine, because of the initiatory disturbances of vision. Migraine is a common affection, and is known among the laity as "blind headache." Gowers asserts that it is often associated with high intellectual ability, and many distinguished scientific men have suffered from it and have furnished careful descriptions of the subjective symptoms.

The symptoms of migraine are so well known that I need not stop to detail them further. My purpose at this time is to discuss, rather, the suggestion put forth by Gowers a number of years ago, and since adopted and defended by numerous other writers and teachers on nervous diseases, that this disease is related to epilepsy. Liveing, loc. cit., had already advanced the theory that the affection is a neurosis in the course of which there occur periodical sensory discharges analogous to the motor discharges of epilepsy, but he did not seem to regard the two diseases as particularly related to each other.

In referring to the pathology of migraine, and especially to its relation to other diseases, Gowers says: "The most important and one of the most frequent of these associations is the relation of migraine to epilepsy. The connection of the diseases is of especial interest because the sensory disturbance of the two has so many common features." He then refers to cases of epileptics in whom migraine was present in themselves or in their ancestors or descendants. He says he has met with a number of cases in which there was both epilepsy and migraine. In some, epilepsy developed after many years of migraine or seemed to grow out of it. In one, the migraine which had existed for years almost disappeared when the fits occurred, and vice versa. In some there were similar sensory symptoms preceding the epilepsy as in migraine.

ALVIN A. HUBBELL, MD
(*NY State J Med* 1901; 1:7-9)

Robert Kenneth Boese, MD, Glen Cove. Died August 6, 1991; age 55. Dr Boese was a 1963 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Surgery. He was a member of the New York Academy of Medicine, the New York Academy of Gastroenterology, the Nassau County Medical Society, and the Medical Society of the State of New York.

Samuel C. Bregande, MD, Syracuse. Died September 28, 1990; age 78. Dr Bregande was a 1937 graduate of the State University of New York Health Science Center at Syracuse, College of Medicine. He was a Diplomate of the American Board of Otolaryngology. His memberships included the New York Academy of Medicine, the American Academy of Otolaryngology, the Onondaga County Medical Society, and the Medical Society of the State of New York.

Melvin Morris Brodie, MD, Brooklyn. Died July 28, 1991; age 94. Dr Brodie was a 1923 graduate of Cornell University Medical College. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Frank Calabro, Jr, MD, Mastic Beach. Died July 26, 1991; age 58. Dr Calabro was a 1961 graduate of the University of Health Science Chicago Medical School. He was a Diplomate of the American Board of Family Practice. He was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Richard S. Cohen, MD, Fishkill. Died August 9, 1991; age 51. Dr Cohen was a 1966 graduate of Albert Einstein College of Medicine of Yeshiva University. He was a Diplomate of the American Board of Internal Medicine. He was a member of the Dutchess County Medical Society and the Medical Society of the State of New York.

Abraham Fine, MD, Plantation, Florida. Died July 19, 1991; age 94. Dr Fine was a 1922 graduate of Cornell University Medical College. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Majer Frankfurt, MD, Roslyn. Died July 15, 1991; age 80. Dr Frankfurt was a 1949 graduate of Medizinische Fakultät, Universität Bern, Bern, Switzerland. He was a Diplomate of the American Board of Ophthalmology. His memberships included the New York Society for Clinical Ophthalmology, the American Academy of Ophthalmology and Otolaryngology, the Pan American Association of Ophthalmology, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Agnes Ophelia Griffin, MD, Brooklyn. Died July 13, 1991; age 94. Dr Griffin was a 1923 graduate of Columbia University College of Physicians and Surgeons. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Harry Goldberg, MD, New Hyde Park. Died December 28, 1990; age 75. Dr Goldberg was a 1942 graduate of the University of Louisville School of Medicine, Louisville, Kentucky. He was a member of the American Geriatrics Society, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

William Edmonds Homan, MD, White Plains. Died July 21, 1991; age 72. Dr Homan was a 1943 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Pediatrics and a Fellow of the American Academy of Pediatrics. He was a member of the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Charles William Jones, MD, Walton. Died August 1, 1991; age 72. Dr Jones was a 1945 graduate of the University of Vermont College of Medicine, Burlington, Vermont. He was a Diplomate of the American Board of Pathology and a Fellow of the American College of Pathologists. His memberships included the New York Pathological Society, the American Society of Clinical Pathologists, the International Academy of Pathology, the Delaware County Medical Society,

and the Medical Society of the State of New York.

Zbigniew Michael Lorenc, MD, Glen Head. Died July 31, 1991; age 75. Dr Lorenc was a 1939 graduate of the University Stefana Batorego Wydział Lekarski, Wilno, Poland. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Mario John Merlino, MD, Staten Island. Died July 24, 1991; age 63. Dr Merlino was a 1969 graduate of Facoltà di Medicina e Chirurgia, Università di Padova, Padova, Italy. He was a member of the Richmond County Medical Society and the Medical Society of the State of New York.

Frank Musacchio, MD, Brooklyn. Died July 25, 1991; age 76. Dr Musacchio was a 1943 graduate of the Medical College of Wisconsin, Milwaukee, Wisconsin. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. His memberships included the New York Cardiological Society, the Pan American Medical Association, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Abraham I. Raskob, MD, Brooklyn. Died July 14, 1991; age 78. Dr Raskob was a 1943 graduate of Middlesex University School of Medicine, Waltham, Massachusetts. He was a Fellow of the American College of Anesthesiologists. His memberships included the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, Inc, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Orin Louia Rogers, MD, Clayton. Died August 10, 1991; age 74. Dr Rogers was a 1947 graduate of the State University of New York Health Science Center at Syracuse, College of Medicine. He was a member of the American Academy of Family Physicians, the Medical Society of the

County of Jefferson, and the Medical Society of the State of New York.

Francis A. Stephens, MD, Glenmont. Died July 24, 1991; age 81. Dr Stephens was a 1935 graduate of the Albany Medical College. He was a member of

the Medical Society of the County of Albany and the Medical Society of the State of New York.

George Abbott Voss, MD, Schenectady. Died February 17, 1991; age 58. Dr Voss was a 1960 graduate of New York

Medical College. He was a Diplomate of the American Board of Surgery and a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Schenectady and the Medical Society of the State of New York.



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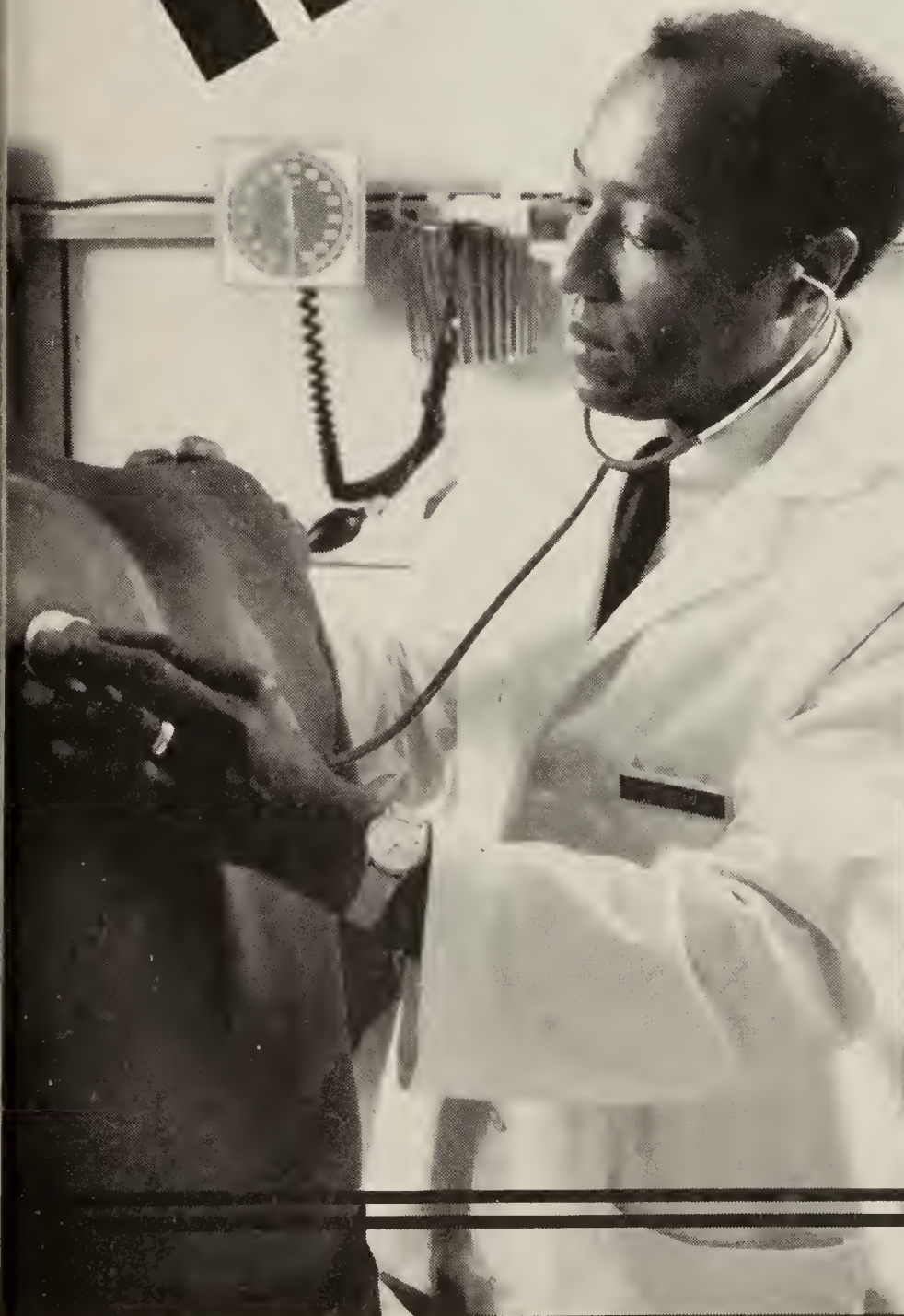
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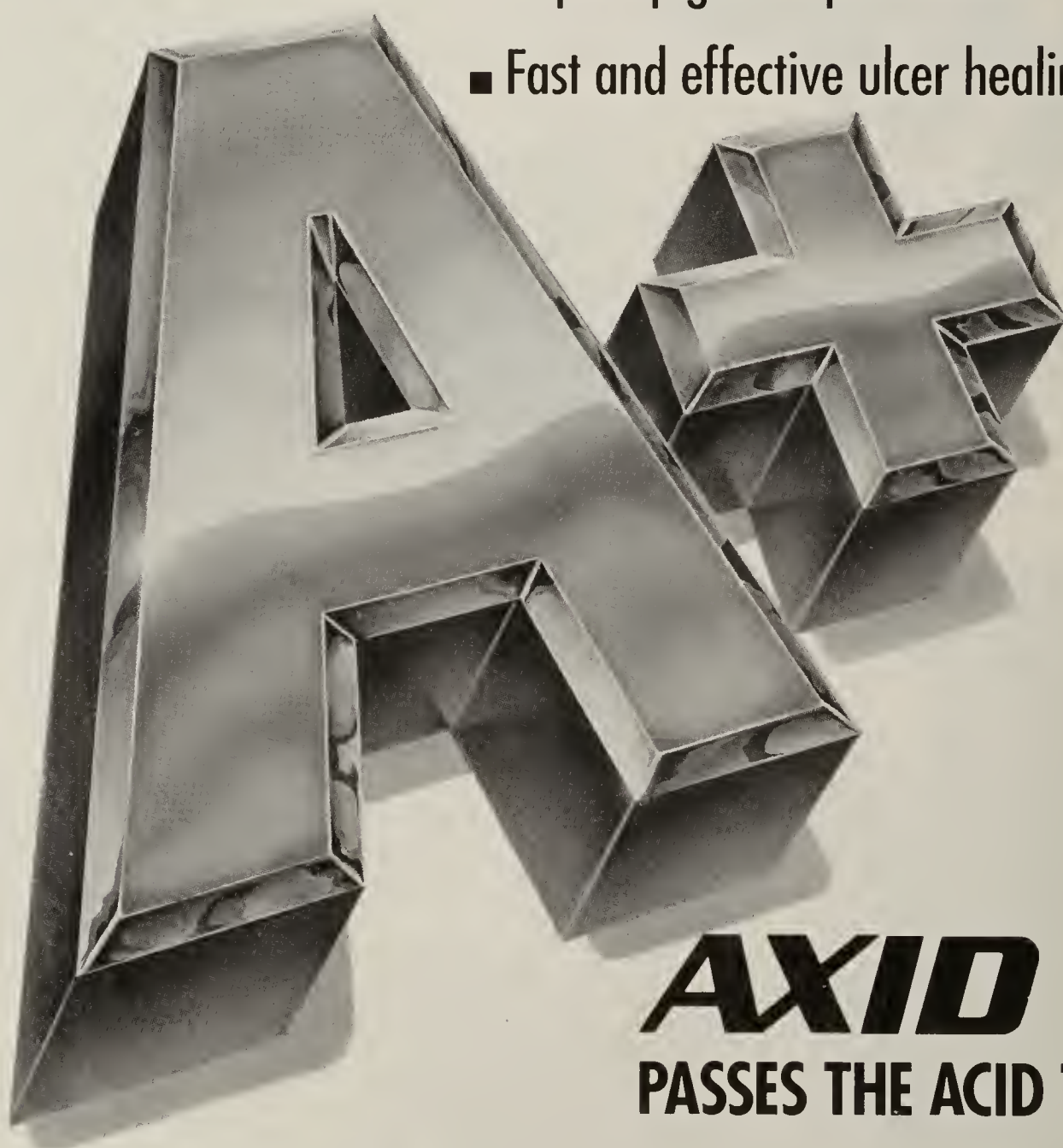
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Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H₂-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.
3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix[®] may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chloridazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H₂-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H₂-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage—Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

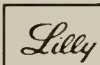
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1. Data on file, Lilly Research Laboratories
2. *Scand J Gastroenterol* 1987;22(suppl 136):61-70
3. *Scand J Gastroenterol* 1987;22(suppl 136):47-55.
4. *Am J Gastroenterol* 1989;84:769-774

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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

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Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

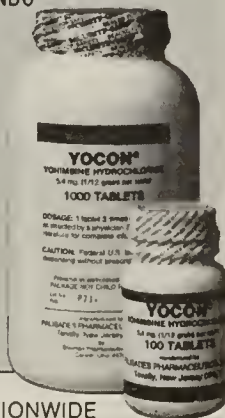
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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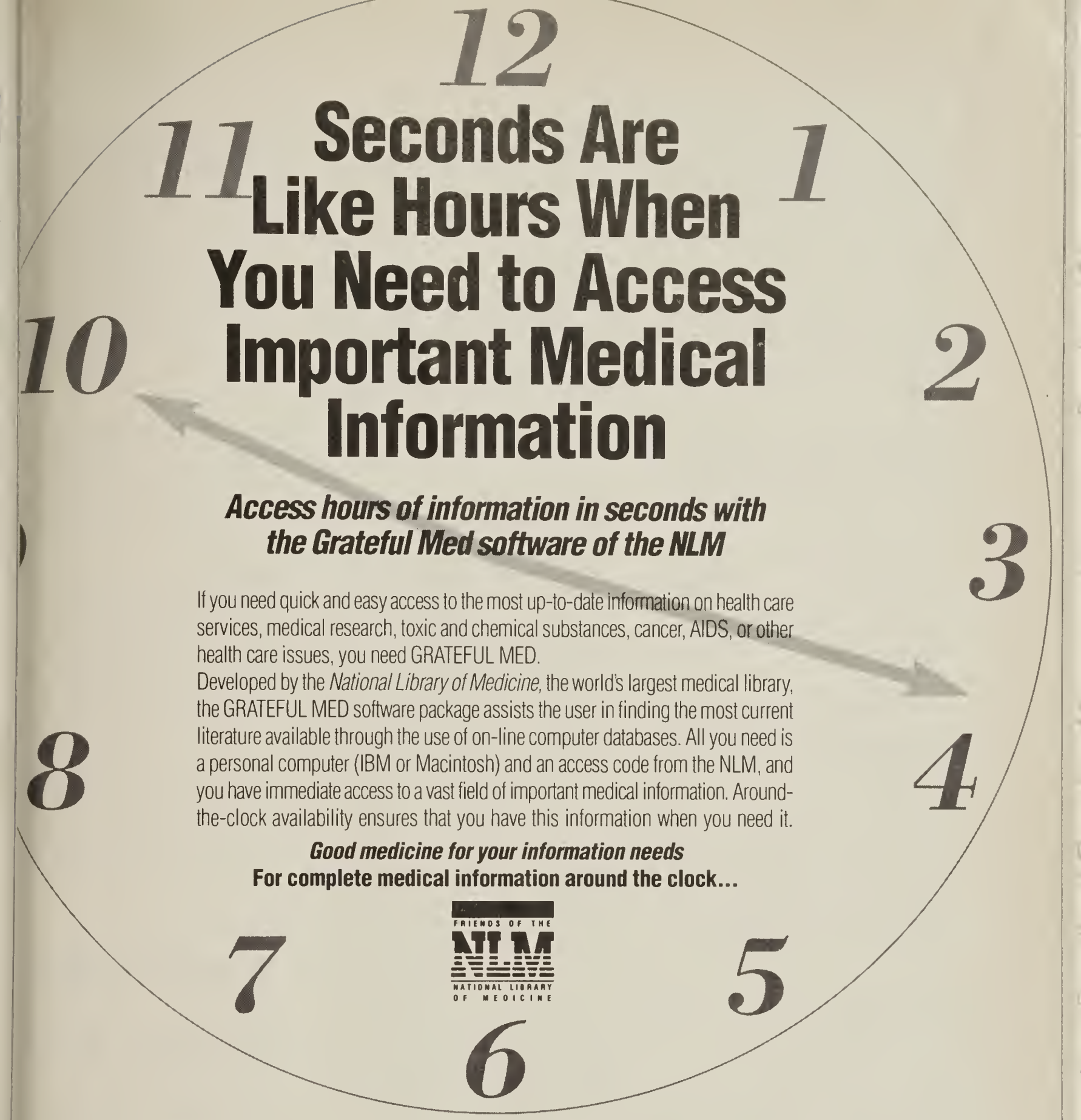
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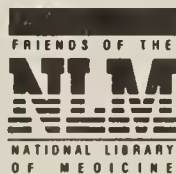
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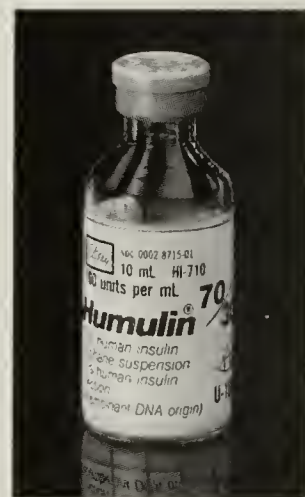
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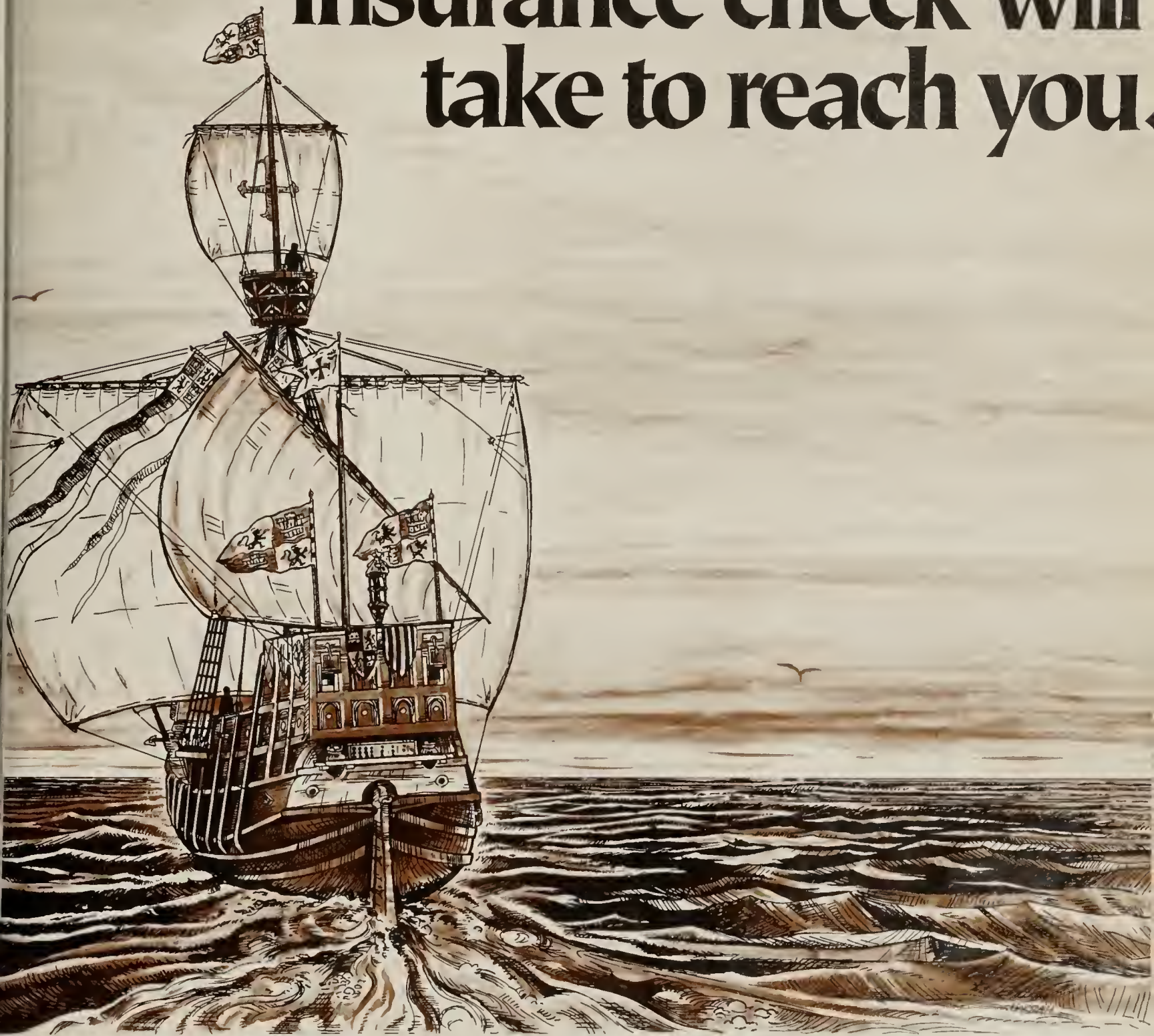
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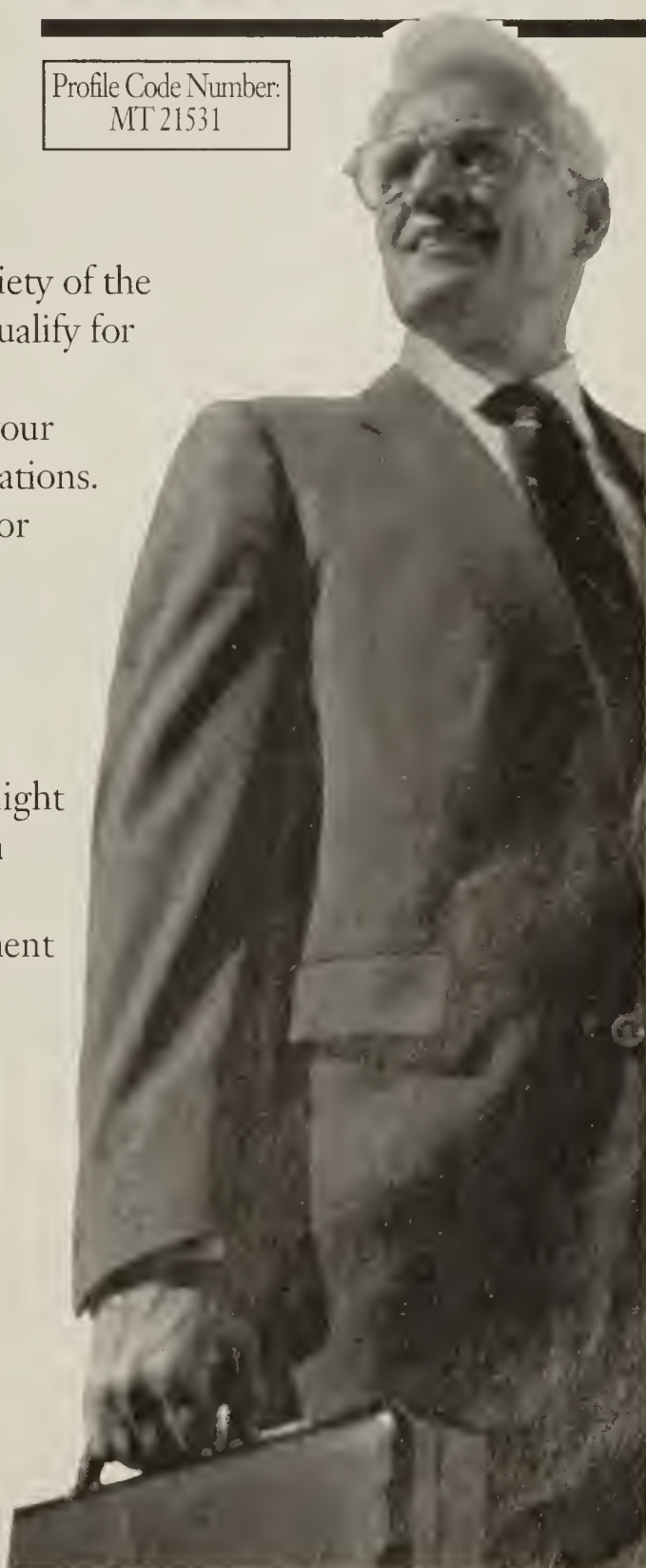
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One Of A Kind



Zantac[®]
ranitidine HCl/Glaxo 150 mg and
300 mg tablets

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/ROCHE

Zantac[®] 150 Tablets
(ranitidine hydrochloride)

Zantac[®] 300 Tablets
(ranitidine hydrochloride)

Zantac[®] Syrup
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac[®] product labeling.

INDICATIONS AND USAGE: Zantac[®] is indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within four weeks.

2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

3. The treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome and systemic mastocytosis).

4. Short-term treatment of active, benign gastric ulcer. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.

5. Treatment of gastroesophageal reflux disease (GERD).

Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy.

In active duodenal ulcer: active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac[®] is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to Zantac[®] therapy does not preclude the presence of gastric malignancy. 2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix[®] may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although recommended doses of Zantac do not inhibit the action of cytochrome P-450 enzymes in the liver, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Headache, sometimes severe, seems to be related to Zantac[®] administration. Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and, rarely, pancreatitis have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, atrioventricular block, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Although controlled studies have shown no antitumor activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac[®] product labeling.)

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac[®] 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac[®] 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac[®] Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in light, light-resistant containers as defined in the USP/NF.

September 1990

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

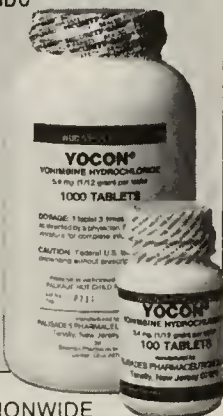
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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JANUARY 1991

AROUND THE STATE

MANHATTAN

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AROUND THE NATION

ARIZONA

Jan 13-17. 11th Annual Postgraduate Course: Uroradiology 1992. Princess Resort Hotel, Scottsdale. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077. Tel: (404) 641-9773.

Jan 16-18. American Academy of Pain Medicine's 1991 Annual Conference. Registry Hotel, Scottsdale. Contact: American Academy of Pain Medicine, 5700 Old Orchard Rd, First Floor, Skokie, ILL 60077. Tel: (708) 966-9510.

Jan 27-31. Psychopharmacology Review: Current Clinical Practice. Westin La Paloma Resort, Tucson. Contact: Continuing Medical Education, Arizona Health Sciences Center, Tucson, Arizona 85724. Tel: (602) 626-7832.

CALIFORNIA

Jan 10-12. Advanced Seminars in Diagnostic Imaging. 15 Cat I Credits. Ritz-Carlton Resort Hotel, Laguna Niguel. **Jan 12-16. Diagnostic Imaging Update: Body Imaging, Mammography, Neuroradiology, and Pediatrics.** 23 1/2 Cat I Credits. Ritz-Carlton Palm

(continued on p 14A)

New York State Journal of Medicine



COMMENTARIES

The current syphilis epidemic in New York State

In 1985, an epidemic of syphilis began in various areas of the United States. In New York State, where reported cases increased threefold between 1985 and 1990, the epidemic has been centered in New York City, in the five counties surrounding the city (Nassau, Suffolk, Orange, Rockland, and Westchester), and in Erie and Monroe counties in the northwestern part of the state. This epidemic, in which close to 14,000 cases of syphilis are now being annually reported in the state, has received scant attention in the press and media and many practicing physicians are unaware of it.

Several communications in this issue of the *Journal* focus on this new and serious epidemic. MacCubbin et al¹ and Ong et al³ present detailed information on the epidemiology of the disease. Rolfs and Schmid⁴ comment on the broader national picture and Levensohn et al⁵ and Novick⁶ provide details and insights into the New York State Department of Health's Syphilis Initiative.

Unlike previous epidemics of syphilis, this one has some unique characteristics.⁷ The majority of those affected are inner-city residents. Poverty, drug use, and anonymous sexual activity are important social determinants, and many cases are associated with human immunodeficiency virus (HIV) infection. Many women are infected because they provide sex for drugs, particularly cocaine, or for money to buy drugs. This is reflected in the shift in the ratio of male to female cases in New York from 1.53 in 1985 to 0.93 in 1990. At the same time that heterosexual transmission was increasing among those involved with drug use, homosexual transmission was decreasing among males. The latter was due in large measure to behavior changes among homosexual males in response to the acquired immunodeficiency syndrome (AIDS) epidemic. Thus, although syphilis in the 1970s and early 1980s was primarily a disease of white homosexual males, by the late 1980s it had become a disease of heterosexual drug users in the inner city.

Congenital syphilis had become rare by 1980 when only 26 cases were reported in New York City and one

outside of the city. In 1990, 1,054 cases were reported in the city, and 91 were reported in the remainder of the state. In New York City, 41% of cases of congenital syphilis are associated with maternal drug use, primarily cocaine. Among mothers who gave birth to infants with congenital syphilis, only a third in New York City are receiving prenatal care.

The patients affected by this epidemic tend to receive their medical care, not in physicians' offices and prenatal care clinics, but in emergency rooms, family planning clinics, drug treatment clinics, and jails. Thus, efforts to reach them cannot uniquely rely on standard methods used to control previous syphilis epidemics.

To control the current epidemic, the New York State and New York City Department of Health undertook a series of interventions in 1990, collectively known as the Syphilis Initiative, detailed by Levensohn et al⁵ and Novick⁶ in this issue of the *Journal*. In addition, in August 1990, Dr David Axelrod, then Commissioner of Health of New York State, established the Metropolitan New York City Area Task Force on Syphilis. The charge to this Task Force was to review the rapidly increasing problem of syphilis in New York City and the five surrounding counties, to examine the adequacy of state and local public health activities related to syphilis, and to recommend further the specific actions needed to combat the epidemic. The recommendations made by this Task Force are presented elsewhere in the *Journal*.⁸

The current syphilis epidemic is being sustained by unusual social determinants. Bringing it under control will require the concerted efforts of physicians, public health officials, medical care institutions, and those most at risk.

PASCAL JAMES IMPERATO, MD

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The opinions expressed in this editorial are those of the author alone and do not constitute an expression of official opinion of the Medical Society of the State of New York.

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The United States syphilis epidemic: Reason for optimism (at least for the moment)

From 1986 to 1990, the incidence of primary and secondary (P&S) syphilis in the US increased dramatically, by 77%, from 11.5 to 20.4 cases per 100,000 persons, the highest rate since 1949. This epidemic has primarily affected inner-city persons, although substantial increases also occurred in areas of the rural South.^{1,2} In both urban and rural areas, the epidemic has largely been confined to heterosexual, often poor, African Americans. Strikingly, the incidence of P&S syphilis among African Americans increased 135% from 1986 to 1990, while decreasing for all other racial and ethnic groups.

National trends are a summation of trends in individual communities; thus, and the national increase reflects multiple outbreaks in many communities throughout the country. In examining the 1986-90 data, rates increased most rapidly in the first year because of outbreaks in large population areas, including New York City, the City of Los Angeles and elsewhere in California, and in southern Florida. The epidemic then "spread" from these earliest affected areas to other areas throughout the US. By 1990, few large cities had been untouched by the epidemic, which was notable for the abruptness with which it struck individual communities. In some areas, case totals increased by twofold from one quarter year to the next.

Substantial effort has been made to identify the causes of the syphilis epidemic; although undoubtedly many factors contributed, several epidemiologic studies support the strong impressions of many disease control workers that the parallel epidemic of crack cocaine use played an important role.⁴⁻⁸ Crack cocaine use probably alters syphilis transmission dynamics by two mechanisms.

First, and the mechanism that has received the most attention, is the crack-related increase of prostitution. This increase occurs because women become addicted to crack cocaine and have multiple sexual encounters in exchange for crack or money needed to purchase the drug. The exchange of sex directly for one dose of drugs or the small amount of money needed to purchase it is an important feature of this type of prostitution. It

indicates how little control these women have over the client-prostitute transaction. Rather than being a business transaction that supports the woman and her drug-use habit, prostitution becomes an integral part of that drug-use habit. This loss of control leads the prostitute, usually a woman, to receive less for each exchange. Consequently, she engages in more client contacts, thus increasing the risk of spreading a sexually transmitted disease (STD).

The second mechanism, an effect of crack addiction on the length of time individuals remain infectious, is more difficult to study and has received less attention. Yet, it may be just as important as unsafe sexual behaviors. Addicted patients may be less likely to notice lesions or to cease sexual activity and seek care even if they notice the lesions. Furthermore, access to health care is already limited for residents of many inner-city and poor rural settings. The demands of supporting a drug-use habit probably combine with poor availability and acceptability of health care, thus prolonging the time people with syphilis remain infectious. Drug use also hinders case-finding by partner notification because users are unwilling or unable to notify sex partners. This in turn prolongs the average duration of infectiousness.

On an optimistic note, preliminary national data indicate that the incidence of P&S syphilis in the US will decrease in 1991. Trends in individual communities provide an additional reason for optimism. In the majority of the communities affected earliest by the P&S epidemic, incidence rates peaked from two to three years after the onset of the epidemic and then either leveled off or began to decline. In some communities, such as Portland, Oregon, rates have declined nearly to the pre-epidemic level. In others, rates have stabilized but remain elevated. Although these data provide reason for optimism, especially for communities where incidence is still on the upswing, it is uncertain whether we should claim victory or merely breathe a sigh of relief.

A sigh of relief may be the appropriate choice, since an examination of long-term syphilis trends suggests that we exercise caution when interpreting current trends. From a nadir in the late 1950s, the incidence of P&S syphilis in the US increased more than fourfold by 1990, from less than 5 to more than 20 cases per 100,000

Address requests for reprints to Information Services, National Center for Prevention Services, (E06), Centers for Disease Control, 1600 Clifton Road, Atlanta, GA 30333.

persons. Throughout this progressive upward trend, prominent cycles are evident with peaks and troughs occurring every 8–10 years. With the notable exception of the decline that began in 1983, caused mostly by favorable behavioral changes among homosexual men in response to the acquired immunodeficiency syndrome (AIDS) epidemic, no clear explanation exists for many of the trend reversals that make up these cycles. The lack of correlation between trends for syphilis and gonorrhea during the late 1980s and earlier periods provides added caution regarding our ability to infer that changes in sexual behavior have occurred from these trends. As for the cycles in syphilis incidence, the lack of correlation between these similarly transmitted infections is largely unexplained.³

Although current trends suggest that for many communities the epidemic has peaked and begun to wane, the overall incidence rate remains high, and prevention of congenital syphilis will require continued vigilance long after the decline of newly acquired infection in adults. Assuming present trends continue, however, an important question will be whether we as a public health and STD control community can claim victory over this epidemic or have merely documented its passage.

On the basis of available evidence, it is difficult to conclude firmly that the public health response has been the most important factor in bringing this epidemic under control. First, the epidemic occurred in spite of vigorous efforts during the mid-to-late 1980s to promote safer sexual behavior. Thus, it is hard to argue that general risk reduction efforts, through counseling and education, have had an important effect in reversing the epidemic.

Second, partner notification has been the focus of most efforts specifically targeted at controlling this epidemic. Partner notification allows detection of infected persons during the incubation period before transmission can occur. Therefore, it is a powerful tool for syphilis control. However, recent experience and several studies have suggested that it is relatively ineffective among the core, drug-using population thought to be important in syphilis spread.^{4,5,10} Thus, although increased emphasis on partner notification undoubtedly prevented many cases, it seems unlikely that partner notification was promoted sufficiently to reverse the increase. The Centers for Disease Control is currently working with several local health departments to evaluate prospectively the effectiveness of partner notification, for both syphilis and HIV.

Third, several innovative intervention efforts have used an understanding of syphilis epidemiology to target high-risk populations. These have included screening at sites of drug use and at locations suggested by information obtained from syphilis patients.^{11,12} Although some of these efforts have been productive, they have usually been small pilot projects, unlikely to have had an important community-wide effect on transmission.

In contrast to these small, targeted efforts, and as described elsewhere in this issue of the *Journal*, the New York State syphilis initiative focused on widespread serologic screening. Since serologic screening is likely to detect most patients during latent, non-infectious stages,

after lesions have already healed, and is unable to detect patients before the the onset of infectiousness, it is not an optimal way to interrupt sexual transmission in the community. In contrast, serologic screening among pregnant and other reproductive age women is an effective way to prevent congenital syphilis, an important goal of the New York State program.

Substantial attention is often paid to determining reasons for an epidemic, but we rarely take the time to examine why epidemics decline. It remains unclear which, if any, of the above described efforts had an important effect on interrupting transmission of *Treponema pallidum* or if some underlying factor affecting transmission, such as patterns of drug use, has changed. At this point, the latter explanation seems more likely. If the pattern of syphilis trends over the past four decades continues and this is merely a temporary "correction" preceding further increases, we might well benefit from a better understanding of what led to the current relief from this epidemic.

The need to understand the decrease is heightened for two reasons. First, syphilis has been a useful marker of sexual behavior important in the spread of HIV. Second, substantial evidence suggests that syphilis and other diseases that cause genital ulcers serve as important co-factors for HIV transmission.¹³ The population currently affected by the syphilis epidemic is probably the US population at highest risk for heterosexual HIV transmission. If syphilis is beginning to decline in this population because of behavior change, it would augur well for decreased risk of HIV transmission. If the decline is merely a cyclic downturn due to unknown reasons, the implication for future HIV transmission is less clear.

It is clear, however, that one potentially powerful intervention has been largely ignored. Since syphilis is spread only when clinical lesions are present, the patient should be our most powerful case-finding ally. This is particularly true for men, for whom infectious lesions should be readily detectable. Less than one third of men and less than 10% of women in the US are detected and treated during the primary stage, which lasts 2–6 weeks, allowing ample time for detection. Among the population most at risk, we need to increase awareness of the disease and its clinical manifestations and to remove the barriers that deter infected persons from seeking and obtaining treatment. We also need to better understand health care seeking behavior and how to improve it. Although partner notification and screening are important interventions with proven benefit, syphilis will become a far less important disease in this country if we are able to make infected persons, their sex partners, and the health care system our allies in fighting this disease.

ROBERT T. ROLFS, MD

GEORGE P. SCHMID, MD

Division of Sexually Transmitted

Diseases/Human Immunodeficiency Virus Prevention

National Center for Prevention Services

Centers for Disease Control

1600 Clifton Rd

Atlanta, GA 30333

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Syphilis: A broad initiative to control New York State's epidemic

Syphilis is epidemic in areas of New York State. In just five years, from 1985 to 1990, the statewide incidence of this preventable disease almost tripled, from 5,120 to 13,997 cases a year. As MacCubbin and other investigators report elsewhere in this issue of the *Journal*,¹ the epicenter of the epidemic is New York City, but a sharply increased incidence has been observed in seven other counties as well. Five of those counties are close to New York City (Nassau, Suffolk, Westchester, Rockland, and Orange); two are in the northwestern part of the state (Erie and Monroe). Suffolk County, on Long Island, experienced a sevenfold increase during this five-year period, reporting 369 cases in 1990.

The gravity of this epidemic is illustrated by the crisis of congenital syphilis in New York State. A decade ago, fewer than 100 cases were reported each year. In 1990, reflecting the increased incidence of syphilis among women of reproductive age, nearly 1,200 infants were born syphilitic. The vast majority (all but 91) of these births were in New York City, but an upward trend in other epidemic counties has also been documented.

The incidence in syphilis among adults in New York State is now comparable to its incidence during the 1950s, when antibiotic treatment was just beginning to control the earlier, long-term epidemic. The current incidence of congenital syphilis is somewhat harder to compare because of changes in the classification scheme, but it is approximately equivalent to that of the early 1940s.

Public health agencies, including New York State Department of Health, recognize an additional hazard of the syphilis epidemic: sexually transmitted diseases (STDs) that cause genital ulcers may increase the risk of infection with the human immunodeficiency virus (HIV). This mechanism of HIV transmission in heterosexual women and men in Africa has been suggested by Kreiss et al.² HIV seroprevalence studies in New York State have shown a greater likelihood of HIV infection among individuals who visit STD clinics and are diagnosed as having syphilis.³

Since syphilis is preventable by penicillin and other antibiotics, every new case, and certainly an epidemic of

new cases, indicates a breakdown in the public health and medical care system. As long ago as 1976, David Rutstein and others⁴ included congenital syphilis and symptomatic early syphilis among the diseases they defined as sentinel health events, which require a "clear-cut, immediate" response. Rutstein and others compared these sentinel health events to airplane crashes, which are routinely investigated to determine the causes and to prevent recurrence. Taking congenital syphilis as a sentinel event, how do we explain 1,200 airplane crashes in a single year in New York State.

The factors that result in congenital syphilis include not only exposure to the pathogen but also complex societal problems. The mothers usually live and become infected in urban areas characterized by substandard schools, lack of job opportunities, frequent exposure to illicit substances of abuse, and inadequate or no prenatal care. These and other associated conditions are conducive to behaviors that increase the risk of infection. The remedy is therefore more complex than simply ensuring the availability of medical treatment.

Even routine preventive measures will not solve the epidemic of congenital syphilis, or the larger syphilis epidemic, because syphilis today is a community problem that is intertwined with drug abuse, poverty, HIV infection, and other STDs. Patients with syphilis tend to receive health care, not in physicians' offices and prenatal care clinics, but in emergency rooms, family planning clinics, drug treatment clinics, and jails.

The community aspect of the syphilis epidemic was recently explored by Aral and Holmes,⁵ who noted that three STDs that have disappeared in most of the industrialized world, syphilis, gonorrhea, and chancroid, are increasing at epidemic rates among urban minorities in the United States. Local syphilis epidemics have been observed in and around New York City, in Philadelphia, Baltimore, and Los Angeles, and in areas of Texas and Florida. Aral and Holmes attributed this epidemic primarily to urban poverty, social disintegration, and the exchange of sex for drugs. For these reasons, they conclude that "innovative programs are needed to focus STD control efforts." The new strategies "should target

not only susceptible high-risk persons, but also entire communities and subgroups with high STD rates."

When Aral and Holmes' article appeared in February 1991, an innovative, community-wide program had long been under way in New York State. As described by MacCubbin and others¹ and by Levensohn and DiFerdinando,⁶ the Syphilis Initiative and earlier measures had been shaped by epidemiologic observations of the state's growing epidemic. Unlike syphilis epidemics in the 1960s, which had included a large component of male-to-male transmission, the current epidemic in New York State is characterized by heterosexual transmission, often associated with use of cocaine or crack and with exchange of sex for drugs.

In mounting a major initiative against this epidemic, the New York State Department of Health chose not to rely solely on community education, outreach, and mobile testing and referral efforts. A special program, which we call the Syphilis Initiative, was conceived and implemented to screen people who are at highest risk by meeting them at all of the facilities where they are likely to appear, including hospitals, emergency rooms, family planning clinics, drug treatment clinics, community health centers, and jails. With screening, follow-up, and referral available at these sites, cases of infectious syphilis could be identified, and contacts could be sought out.

The Syphilis Initiative was implemented in New York City and the other seven epidemic counties of New York State in 1990. It required the combined efforts of state and local health departments and a variety of health care providers, who were notified of the campaign and its importance and were encouraged to participate. In the first seven months, more than 145,000 individuals were screened, and nearly 4,000 (2.74%) of these specimens were reactive. In hospitals, the positivity rate was 2.2%; in jails it reached 5.6%. Not all positive screening specimens, of course, represent new cases of infectious syphilis. Further evaluation of the results is difficult

because adequate follow-up data could not be collected with the existing data system.

Within a short period of time, this massive testing appears to have had an impact on the epidemic. To some extent, it succeeded in identifying cases of infectious syphilis that would not otherwise have been found. Equally important, it alerted health providers throughout the state of the urgency of assessing patients for syphilis as part of every examination in emergency rooms, every clinic visit, and every hospital or jail admission.

Control of the syphilis epidemic in New York State must continue along multiple channels. Former Commissioner of Health, Dr David Axelrod, created a New York City Metropolitan Area Task Force on Syphilis, including professionals from New York City and the nearby epidemic counties, to address all relevant aspects of the epidemic, and formulate comprehensive recommendations. The task force concluded that primary prevention, education of providers, and improved prenatal services are vitally important but not in themselves sufficient for epidemic control. A community-wide effort, such as the Syphilis Initiative, is also essential.

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Syphilis: The epidemiology of change

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After several years of relative quiescence, syphilis re-emerged nationally in 1987 in epidemic proportions, primarily in three states, New York, California, and Florida.¹ In New York State, this disease now strains the resources allocated for its control.

Syphilis is caused by a bacterial spirochete, *Treponema pallidum*, and is acquired either through sexual contact or through transmission in utero from mother to fetus. The disease's manifestations are so diverse that syphilis has been called "the great imposter" for its ability to mimic other diseases. Syphilis occurs in three stages, with the initial (primary) stage being characterized by a chancre or indurated, painless sore, usually in the genital area. The chancre, when left untreated, will disappear within 3–6 weeks when, at about this same time, the symptoms of the secondary stage appear. Secondary symptoms may include body rash, general lymphadenopathy, and genital condylomata lata. After this stage of symptoms, the disease is characterized as latent, although secondary symptoms may reappear for up to 1 year. Without therapy an estimated one third of those infected will eventually develop symptomatic tertiary syphilis,² with associated damage to the nervous, cardiovascular, and musculoskeletal systems.

Treponema pallidum will also cross the placenta of an infected pregnant female causing congenital infection. Such infection can result in miscarriage, stillbirth, premature delivery, a baby born with clinical signs of secondary syphilis, or an asymptomatic infant. Babies who survive can suffer bone deformities or brain or nervous system damage.

The risk of such adverse birth events is directly related to the stage of the mother's syphilis. Women with untreated primary or secondary syphilis during pregnancy will inevitably deliver an infected infant. The longer the mother has had the infection, the lower the chance of fetal infection. The earlier in pregnancy that syphilis is treated, the greater the chance that the infant will be born disease-free. Infection can be acquired anytime during pregnancy, but a fetal immune response is not detectable until 18 weeks.³

The diagnosis of both acquired and congenital syphilis is most commonly obtained through the use of serologic

testing (nontreponemal and treponemal) combined with a history and physical examination. Penicillin is the drug of choice for syphilis, and there is no documented resistance of the organism to this therapy. Treatment is related to the duration of disease. Syphilis of indeterminate or more than 1-year duration requires the administration of therapy on three occasions, whereas primary, secondary, and latent syphilis of less than 1-year duration is treatable in a single dose.⁴

EPIDEMIOLOGY

Traditionally, the study of epidemiology focuses on three concepts: persons, place, and time. The epidemiology of syphilis has radically changed over time. The organism is easily killed, yet the disease eludes eradication. As syphilis decreases in one population, it appears in yet another.

Persons. In the post-war years of 1946–1947, acquired syphilis reached its highest levels ever in New York State, with early (primary, secondary, and early latent) syphilis cases totaling almost 14,000 per year. Subsequently, in the penicillin era, early syphilis decreased until 1960, when the state case load averaged only 4,000. The number of cases peaked in 1964 at 7,500 and decreased after that.⁵

Statewide data from 1975–1980 showed a 39% decrease in reported cases of early syphilis (Fig 1,2). During this time period, the information from testing and partner notification efforts indicated that the disease was occurring primarily in white homosexual males. Data from Monroe County interviews for 1980 and 1990

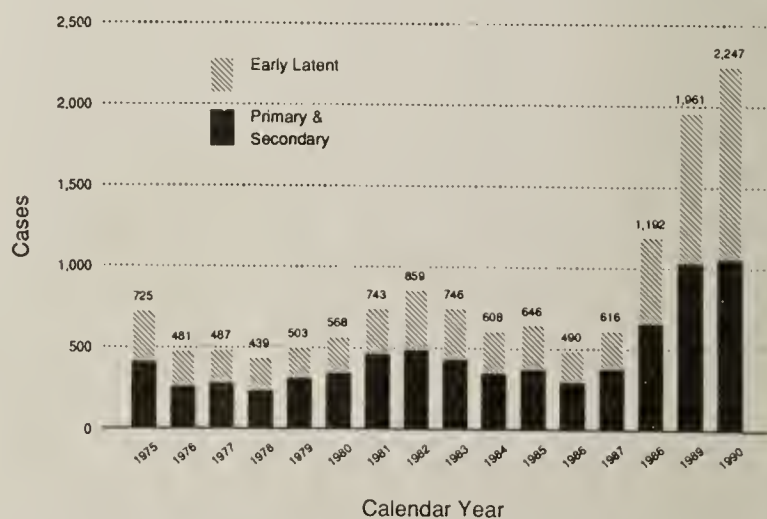


FIGURE 1. Early syphilis, New York City, 1975–1990.

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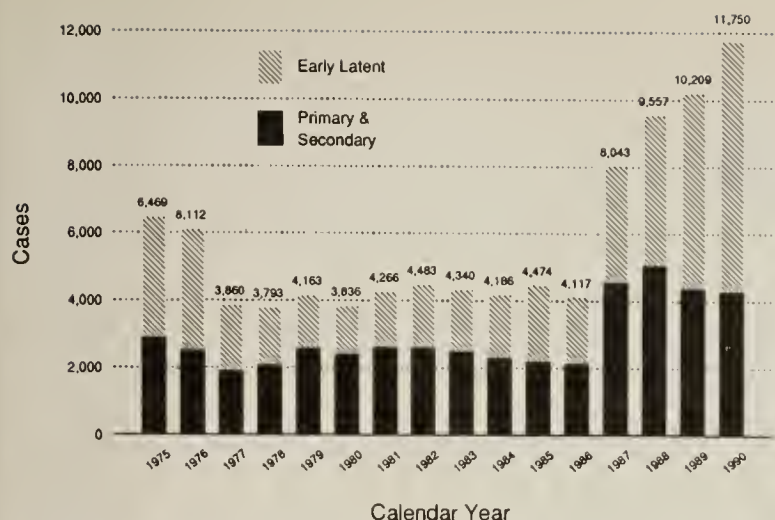


FIGURE 2. Early syphilis, New York State exclusive of New York City, 1975–1990.

demonstrate the shift in sexual preferences of male syphilis cases (Fig 3).

Between 1981 and 1986, the number of annual cases statewide decreased 5%. The number of cases in the intervening years varied from 4,404 in 1980, to a high of 5,342 in 1982, and declining from 5,120 in 1985 to 4,607 in 1986. The period from 1986 to 1990, with a staggering threefold increase to 13,997 cases, is seen as a pivotal point in the syphilis epidemic. This totally unexpected rise in reported cases heralded the advent of the newest phase of the epidemic.

The ratio of male-to-female cases changed during the 1980s (Table I). New York City case data in 1986 showed a ratio of 1.90 infected males per female case. The ratio then declined steadily to 0.93 in 1990. Outside New York City, the ratio dropped from 4.03 infected males-per-female case in 1980 to 0.99 males per female in 1990. This change in the ratio clearly demonstrates the shift from homosexual to heterosexual transmission as more women contract the disease.

This increase in cases among females presents added difficulty in the use of routine contact tracing to control the spread of the disease. When the disease is predominantly in the male population, detection frequently takes place early in the primary (chancre) stage, as the male will often seek help after detecting a genital sore. However, since the chancre in the female is often in the vaginal/cervical areas, the infection may not be detected until much later when the disease has progressed to either secondary or early latent stages. Thus, the time for spread of the untreated disease is greater for females than males. In 1990, in New York State, only 9% of

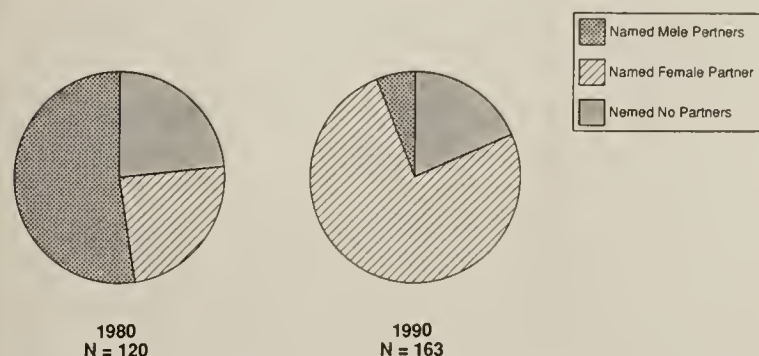


FIGURE 3. Sexual preference of men infected with syphilis interviewed in Monroe County, 1980 and 1990.

TABLE I. Early Syphilis Cases: Male to Female Ratio, New York State, 1985–1990

Year	New York State	
	New York City	Exclusive of New York City
1985	1.53	2.23
1986	1.90	2.24
1987	1.40	1.31
1988	1.22	1.13
1989	0.96	1.07
1990	0.93	0.99

females, as opposed to 25% of males, with syphilis, had their disease detected in the primary stage.⁶ Although the percentage of cases detected in the secondary stage was comparable for males and females (20% and 22%, respectively), the vast majority of female cases (68%) were not detected until the early latent stage.

The racial/ethnic distribution of cases has shifted from white homosexual males to predominantly black heterosexual males and females. In 1990, two thirds of the patients in New York City, as well as those in the rest of the state, were black (Table II). While Hispanic cases account for over 18% of New York City cases, Hispanics outside New York City represent the least infected group. The race/gender shift has also been seen nationally. The Centers for Disease Control recently reported a major change in incidence rates of primary and secondary syphilis during the 1980s. From 1985 through 1990, incidence rates increased 126% for black men and 231% for black women. No other racial/ethnic group demonstrated a similar trend.⁷

The age of syphilis patients has increased as the epidemic has progressed (Fig 4). Whereas the ratios of males 20–29-years old compared with those 0–19-years old were nearly identical in 1985 and 1990, the ratio of males 30–39-years old compared with those 20–29-years old increased from 0.8:1 in 1985 to nearly 1:1 in 1990. Comparisons in females, however, did not show a similar pattern. In females, the ratio of 20–29-year old cases to 0–19-year-old cases was 3.8:1 in 1985 and 5.2:1 in 1990. In the comparison of 30–39-year-old females to 20–29-year-old females, the ratio only increased from 0.5:1 in 1985 to 0.6:1 in 1990.

The demographics of the syphilis epidemic are clearly reflected in the population of women who delivered infants with congenital syphilis in New York State in 1990. In New York City, 41% of congenital syphilis cases, and in upstate New York (New York State exclusive of New York City), 43% of cases were associated with maternal drug abuse (primarily cocaine). Of

TABLE II. Racial/Ethnic Distribution of Primary and Secondary Syphilis, New York State, 1990

Race/Ethnicity	New York State		
	New York City	Exclusive of New York City	Total State
White	3.8%	17.5%	6.6%
Black	64.9%	66.4%	65.2%
Hispanic	18.6%	7.5%	16.4%
Other/unknown	12.7%	8.6%	11.8%

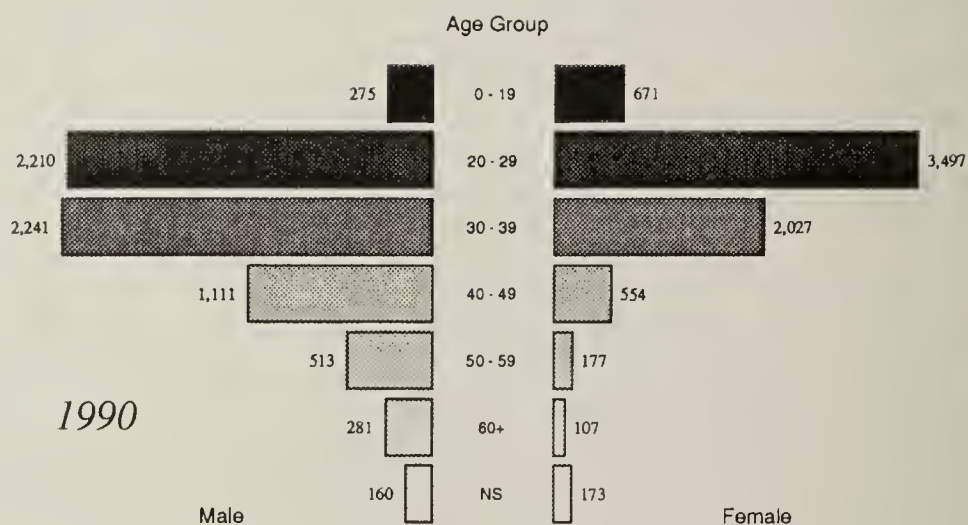
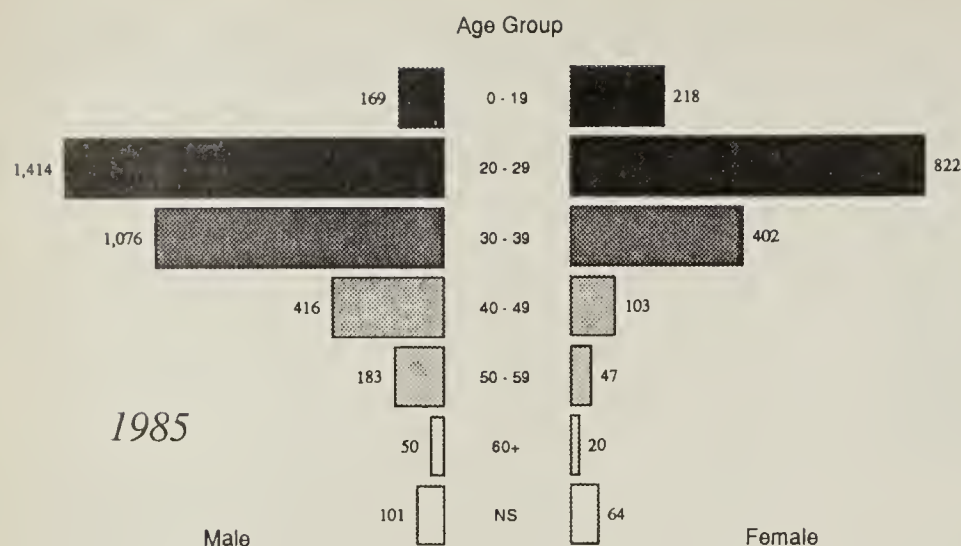


FIGURE 4. Age shift in incidence of early syphilis in New York City, 1985–1990.

New York City mothers, 61% were black, as were 77% of upstate New York mothers. Few of the mothers were married (New York City, 11%; upstate, 17%), and a substantial number had received no prenatal care (New York City, 66%; upstate, 35%). Thirteen percent of New York City mothers were teenagers, whereas 18% of upstate mothers were teens. The upstate percentage reflects an increase from 1989, when only 7% were less than 20 years old. There is concern that congenital syphilis births to teenagers may be on the rise in some areas; of the 17 congenital syphilis cases reported thus far for 1991 for Nassau and Suffolk counties, eight (47%) are to teenage mothers.^{5,8}

Place. In the current epidemic, the vast majority of cases continue to be found in New York City. The ratio of New York City cases-to-cases in the rest of the state declined steadily from 13:1 in 1976 to 5:1 in 1982. However, the case ratio began to increase at that time, peaking again at 13:1 in 1987. The ratio began a downward trend after 1987 but has not approached 1:1.

Outside New York City, most cases have been reported from counties close to New York City. Epidemic counties closest to New York City included Nassau, Suffolk, Westchester, Orange, and Rockland. More recently, two other counties in the western part of the state, Erie and Monroe, were also considered epidemic counties. The majority of cases in these two counties are found in the major metropolitan areas of Buffalo and Rochester, respectively.

Time. The study of syphilis over time reveals trends coincidental with societal changes. The 1960s increase in heterosexual transmission was linked to the sexual revolution of that decade, the widespread use of birth control pills rather than condoms, and sexual permissiveness. The early 1980s witnessed the rapid emergence of human immunodeficiency virus (HIV) infection and AIDS, which occurred primarily in homosexual males. State, local, and community agencies mounted major educational campaigns regarding adoption of safer sexual practices as a means of reducing risk for exposure to HIV.

These early educational campaigns targeted homosexual males. The distribution of HIV infection in New York State by risk factors has demonstrated a shift over time from primarily homosexual males to more cases in intravenous drug users than in any other risk group.⁹ It is believed that a shift in the behavioral practices of the homosexual population was responsible for the shift in case distribution. At the same time as this behavioral shift is believed to have occurred, the cases of syphilis in homosexual white males began to decline, giving further credence to the belief that behavioral changes had occurred.

Crack cocaine became widely available in major US cities, including New York City, in 1986. The upstate counties, predominantly those close to New York City, experienced an increase in crack cocaine usage within the year. Crack users most at risk for exposure to syphilis

and for ongoing infection were the disadvantaged, those facing poverty, those with low educational levels, and those with minimal access to mainstream health care services. In 1988 in Suffolk County, 226 (80%) of 281 persons with early syphilis who were interviewed were either prostitutes who used crack or street level drug dealers/users. Another 27 cases (9.6%) had had sexual contact with drug users/dealers. Fully 90% of the syphilis in Suffolk County that year was directly linked with the street drug trade.¹⁰

Both syphilis and AIDS therefore are now afflicting primarily the heterosexual population, especially those of poor social circumstances and those engaging in prostitution or drug usage, especially crack. Unfortunately, the timing could not have been worse for the convergence of crack use, increased frequency of syphilis, and the rising tide of HIV infection. Syphilis causes genital ulcers, which can facilitate entry of the HIV virus into the body; T-cells and macrophages gather at the site of the ulcer—the same types of cells that help facilitate entry of the HIV virus into the body.¹¹ Both diseases are sexually transmitted, and given the added sexual intensity associated with crack use, many anonymous partners may be exposed to one or both infections in a relatively short period of time. In blind seroprevalence testing of clients in sexually transmitted disease clinics in New York State, it has been observed that patients who test positive for syphilis are 2.5 times more likely to test positive for HIV than are those with negative syphilis serology.¹²

Reports in the literature of difficulties of diagnosis and management of both HIV and syphilis in the presence of the other infection are becoming more frequent. For these reasons, it is now considered essential that persons with syphilis be tested for HIV, and persons who are HIV-positive have a syphilis test.

Although testing for syphilis is not uniform in prisons, jails, and other correctional facilities across New York State, there is compelling evidence that such sites offer high return value for syphilis testing. In a recent study of the Nassau County Jail, Heimberger et al¹³ showed that this facility accounted for 20% of the county's syphilis morbidity. This study further indicated that such testing was extremely cost efficient, in that one of every two positive blood samples drawn from inmates revealed a newly discovered case of syphilis.

Studying the congenital syphilis cases over time is also revealing. As the disease strikes more women, the opportunity for mother-to-fetus transmission increases. The major increase in congenital cases occurred between 1987 and 1988 (Table III), at the same time as the increase in syphilis among heterosexuals. Likewise, the following year saw the rise in upstate congenital syphilis cases. Between 1987 and 1990, the annual number of congenital syphilis cases increased eightfold statewide.

POPULATION AND BEHAVIOR CHANGES

During the 1970s and early 1980s, while the number of early syphilis cases was on the decline, the identifiable populations at risk were those most likely to have regular contact with varying health service facilities. Diagnosis and treatment followed a normal pattern. Cooperation

TABLE III. Reported Cases of Congenital Syphilis, New York State, 1980–1990

Year	New York State		Total New York State
	New York City	Exclusive of New York City	
1980	26	1	27
1981	34	2	36
1982	11	1	12
1983	18	1	19
1984	41	0	41
1985	58	1	59
1986	56	1	57
1987	142	3	145
1988	357	20	377
1989	1,017	76	1,093
1990	1,051	91	1,142

of syphilis clients led to a reasonably successful partner notification system, which in turn allowed health care workers to contain the disease from spreading beyond the defined population.

A major problem encountered with the shift in the case population in the late 1980s was identification of cases and sexual contacts. Traditional methods became ineffective. Members of the new at-risk population did not regularly avail themselves of standard health care services. A large portion of at-risk pregnant women had little or no prenatal care before delivery. Health service systems designed to work efficiently with the former at-risk population were not successful in reaching the new at-risk population. Innovative approaches were needed to reach those in need of services.

A second problem encountered in this new wave of syphilis cases was the association of crack use and anonymous sex. Many infected patients could not provide the information necessary for the identification of sexual partners because of the anonymous nature of sexual contacts. Others were unwilling to name sexual contacts because of the sex-for-drugs connection and fear of exposing drug contacts.

CONTROL STRATEGIES

An early approach to the control of the current epidemic was designed to prevent transmission from mother to fetus. Congenital syphilis is a preventable infection; it was believed that adequate prenatal care would ensure detection of almost all infected women. New York State has long required that every woman being seen by a physician at the first visit during pregnancy have blood drawn and tested for syphilis. Routine third trimester testing is recommended in high-risk women because some women become infected late in pregnancy. However, this system failed to help the new population of infected pregnant women who had received little or no prenatal care.

Effective December 6, 1989, New York State mandated that every newborn have a blood sample taken from the umbilical cord unless the body blood of the mother was tested at the time of delivery. Syphilis testing in the newborn allows for early diagnosis and antibiotic treatment, as well as identification of the infected mother. However, this major effort to identify and treat

pregnant women is ineffective in containing the epidemic in males or in females who are not pregnant. As Levensohn et al¹⁴ describe the syphilis initiative, it was designed to increase the effectiveness of case ascertainment methods in New York City and those counties designated as epidemic counties.

On the basis of lack of success of traditional control strategies and the most current epidemiologic analysis of the epidemic, New York State fundamentally altered its syphilis disease control strategy. Emphasis would now be placed on transforming the health delivery, social services, and criminal justice systems in the targeted counties into syphilis screening providers. In essence, as high-risk persons came into contact with these systems as part of their daily existence, they would be offered testing for syphilis.

In May 1990, then Commissioner of Health Dr David Axelrod sent letters to each hospital director in each epidemic county suggesting that routine syphilis testing be initiated. The commissioner recommended offering screening to all new admissions and emergency room patients 15–45 years of age. Special emphasis on medical histories and physical examination was also recommended. In addition, the commissioner declared that, in all epidemic counties, routine testing for syphilis was now the standard of care required. The standard of care designation enables Department of Health regulators to review hospitals' compliance and to cite facilities that fail to maintain that standard.

As the syphilis epidemic continues to evolve, the New York State Department of Health must also change its response. Current efforts have been implemented to enhance patient knowledge and risk reduction behaviors

through educational efforts and to identify earlier those infected individuals who do not voluntarily seek screening for sexually transmitted diseases. Continued monitoring of the progress of this epidemic is also in place. As additional changes in the epidemic are detected, modifications to the present programs will be implemented.

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Congenital syphilis in New York City: 1985–1990

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In 1990, New York City continued to experience an increased incidence of reported congenital syphilis. However, the increase from 1989 to 1990 was considerably smaller than those reported in the few previous years (Fig 1).

SURVEILLANCE

The Bureau of Sexually Transmitted Diseases (STD) Control improved surveillance of lower syphilis morbidity hospitals by using senior public health advisor staff to cover additional sites. Lower morbidity hospitals (formerly called passive hospitals) are now visited a minimum of once a month to perform laboratory log reviews/audits. This activity includes monitoring and reporting of infant, adult, and cerebrospinal fluid (CSF) Venereal Disease Research Laboratory (VDRL) serologies. The Public Health Advisor staff then investigates cases of suspected congenital syphilis. Liaison staff were redeployed to 23 select high morbidity facilities on a more frequent basis to expedite rapid identification and follow-up of cases. Currently, a total of 51 New York City (NYC) facilities (including all NYC birthing hospitals) are monitored. A total of 43 (84%) facilities generated suspected congenital cases investigation reports.

The NYC Department of Health (DOH) used the current Centers for Disease Control (CDC) Surveillance definition for congenital syphilis. NYC is one of the few project areas using this criteria. However, CDC is currently attempting to ensure national uniformity for congenital syphilis reporting.

Analysis of maternal residence among the five boroughs of New York City reveals that the borough of Brooklyn continues to be the major source of reported congenital syphilis mothers, followed by the Bronx, Manhattan, Queens, and Staten Island (Table I). In 1990, DOH surveillance from the Bronx improved, resulting in that borough surpassing Manhattan for reported congenital syphilis morbidity.

In spite of the current concern of teenage pregnancies, relatively few cases of congenital syphilis are reported involving teenage mothers (12% in 1990) (Table II). The age distribution of infected mothers correlates with the age distribution of early syphilis cases in adult females. The age group 21 through 30 accounted

for 67% of the cases reported in 1989 and 64% of the cases reported in 1990 (Fig 2).

The racial distribution of congenital syphilis continued to be 71% and 72% black and 26% and 23% Hispanic in 1989 and 1990, respectively. White mothers have continued to represent less than 5% of reported compatible congenital syphilis cases.

Unmarried mothers are at an increased risk of giving birth to syphilis-infected infants. In 1989, 88% of the women who gave birth to infected infants were single versus 89% in 1990. Our data do not permit a clear determination as to whether this is due to increased risk of infection of single women versus married or to decreased prenatal care for single women versus married.

Substance abuse occurs frequently among women identified as delivering infected infants (Fig 3). During 1990, 41% of infected mothers admitted to cocaine usage. Although the percentage of infected mothers admitting to cocaine use has remained stable over the past two years, the Bureau of STD Control's data indicate an increased usage of alternative drugs such as alcohol and marijuana. Admitted abuse of alcohol, for example, was reported for 52 (5%) of mothers in 1989 versus 164 (16%) of mothers in 1990.

The lack of prenatal care is significantly associated with syphilis infection in newborns. In 1990, 47% of the mothers of infected infants reported no prenatal care (Fig 4).

Reported maternal stage of syphilis diagnoses for 1990 revealed a slight shift toward increased early latent syphilis of less than a year's duration and decreased primary and secondary syphilis diagnoses compared with 1989. The stage of syphilis reported for mothers reflects the stage at time of last known treatment (Fig 5).

Comparing 1989 and 1990 data, currently there is a greater percentage of mothers being adequately treated before hospital discharge. In 1990, 74% of all women who gave birth to infected infants received appropriate treatment before hospital release; this compares with 53% for 1989. There is no significant variance in gender for congenital-syphilis-infected infants, males 544 (52%) and females 507 (48%). Infants infected with syphilis are at greater risk of prematurity and low birth weight.

The NYC DOH investigation reports for suspected congenital syphilis cases indicated that in 1990, 73% of all infected infants were asymptomatic versus 84% in 1989. This apparent decrease reflects definitional changes separating elevated CSF protein or cell count cases

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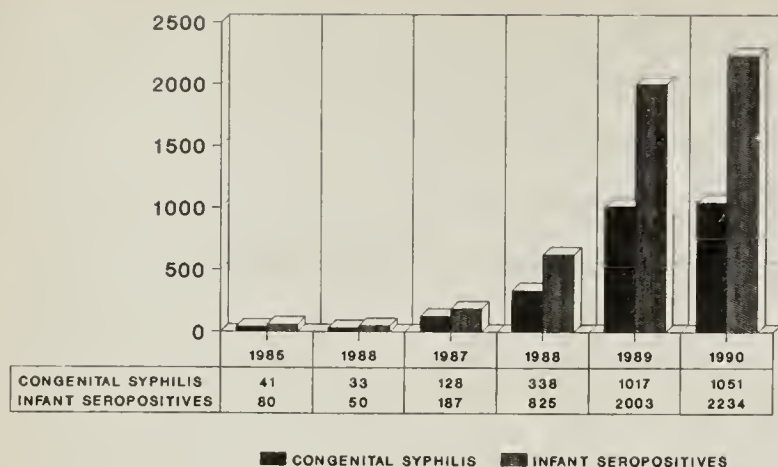
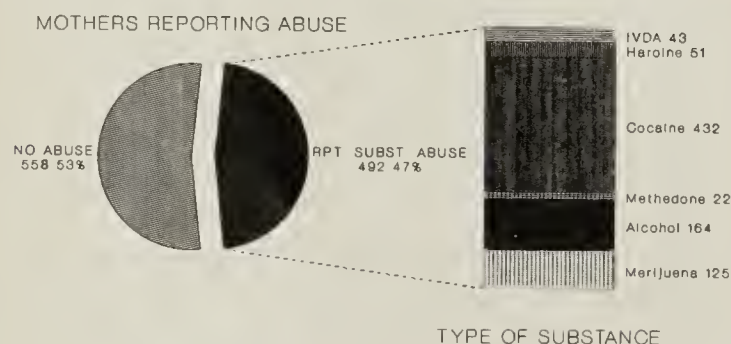


FIGURE 1. Reported congenital syphilis and seropositive infants, NYC: 1985-1990.

(negative CSF-VDRL) from other asymptomatic infants. In 1990, 13% of presumptive/compatible cases met criteria for elevated CSF protein or cell count and were not classified as asymptomatic as they would have been under the 1989 criteria (Table III).

There were 43 syphilis-associated stillbirths reported in 1990 and 11 neonatal deaths for an overall morbidity rate of 5.1% among all compatible cases classified. This compares with the reported 5.5% morbidity rate for 1989 with 49 stillbirths and 7 neonatal deaths.

Data for 1990 indicate that 69% of all infected infants received adequate treatment before hospital release; this compares with 83% in 1989 (Table IV). The CDC treatment guidelines for infants congenitally infected with syphilis were changed during September of 1989. The change involved increasing the dosage of aqueous penicillin from 50,000 U/kg/day to 100,000-150,000 U/kg/day. The data indicate that many physicians continue to prescribe at the lower dose; 11% of the infants



*SOME MOTHERS REPORTED ABUSE OF MULTIPLE SUBSTANCES.

FIGURE 2. Substance abuse reported* by mothers giving birth to infants with presumptive congenital syphilis: 1990.

TABLE I. Geographic Breakdown (Based on Home Zip Code) Congenital Syphilis Presumptive Cases

	Number of Cases	Percentage of Total Cases	Percentage of Known Cases
Bronx	199	19	21
Brooklyn	437	42	45
Manhattan	197	19	20
Queens	125	12	13
Staten Island	9	1	1
Unknown	84	8	—
Total	1051	100	100

TABLE II. Maternal Age at Delivery CS Presumptive Cases

Age Group	Number of Cases	Percentage of Total Cases	Percentage of Known Cases
<15	1	<1	<1
15-20	131	12	13
21-25	312	30	32
26-30	308	29	32
31-35	156	15	16
36-40	51	5	5
40	12	1	1
Unknown	80	8	—
Total	1051	100	100

received this previously accepted treatment. For field investigation purposes and for this report, these infants were considered suboptimally treated and thus requiring evidence of appropriate serologic response.

SUMMARY

The Bureau of STD Control continues to combat NYC's epidemic of congenital syphilis. The demographic profile of this population has remained constant with only a clearer identification of previously reported

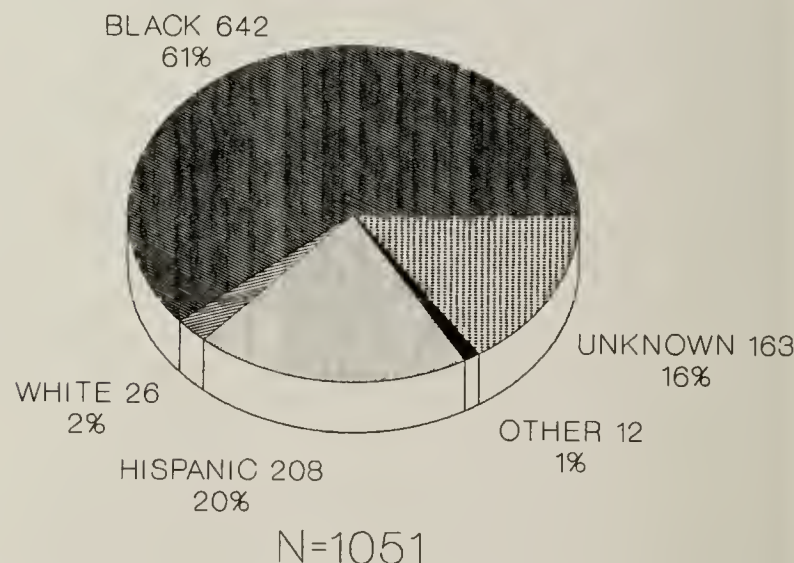


FIGURE 3. Confirmed congenital syphilis by reported ethnic group of mother, NYC: 1990.

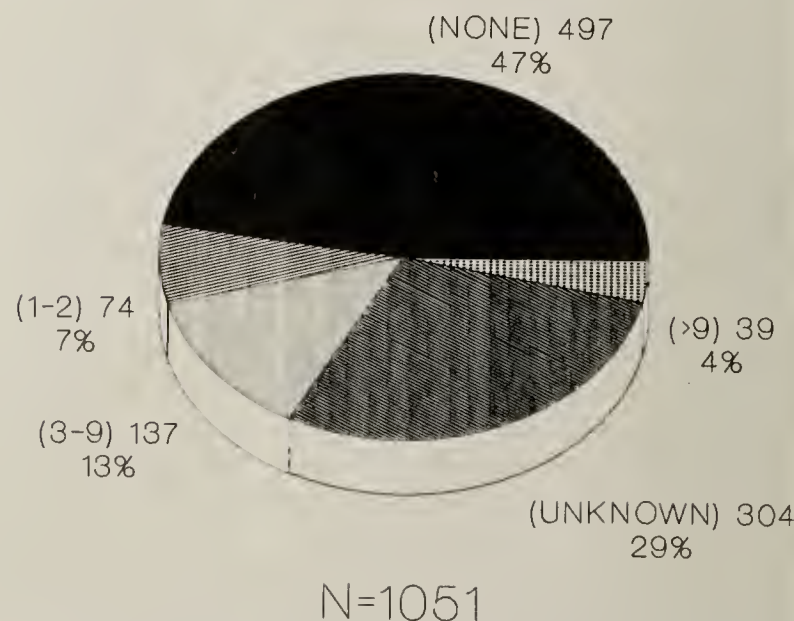
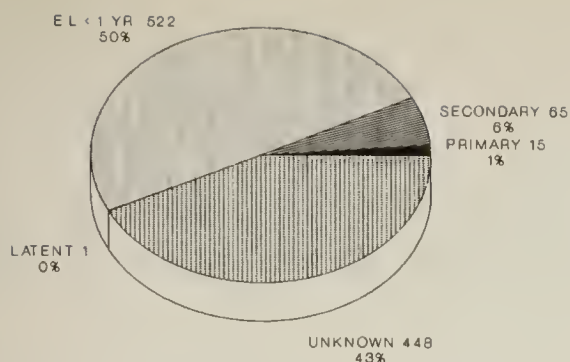


FIGURE 4. Number of prenatal visits by women giving birth to infants with presumptive congenital syphilis: 1990.



MOTHERS OF CASES REPORTED FOR 1990
N=1051

FIGURE 5. Mothers giving birth to infants with congenital syphilis by stage of disease at time of mother's treatment.

TABLE III. Congenital Syphilis Diagnostic Breakdown CS Presumptive Cases

	Number of Cases	Percentage of Total Cases
Asymptomatic (no findings)	771	73
Stillborn	43	4
Symptomatic	64	6
CSF VDRL positive	34	3
Abnormal CSF prot/wbc	139	13
Total	1051	100

risk factors: most notably poor prenatal care and substance abuse. There is a suggestion of a plateau having

TABLE IV. Infant Treatment CS Presumptive Cases

	Number of Cases	Percentage of Total Cases
Total adeq.	718	69
PenG50*	111	11
Benz50*	43	4
Inadequate	35	3
None	117	11
Unknown	27	3
Total	1051	100

*Penicillin G 50,000 U/kg/day and Benzathine penicillin were considered acceptable for treatment of congenital syphilis until the September 1989 CDC Treatment Guidelines were issued. Benzathine 50,000 U/kg is only recommended for fully evaluated asymptomatic infants (normal lumbar puncture and long bone films) whose mothers were treated previous to delivery and lack evidence of relapse or reinfection.

occurred in adult and congenital syphilis, possibly caused by saturation effect on the high-risk population. During the period 1989 through 1990, the rates for cocaine/crack use have remained relatively constant among mothers infected with syphilis. A recent study by the Division of Substance Abuse Services of New York State school-age children demonstrated a drop in cocaine use from 14% in 1983 to 6%. If a similar decline is seen in substance abuse in other age groups, the rate of congenital syphilis may diminish.¹

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Early syphilis in New York City: 1985–1990

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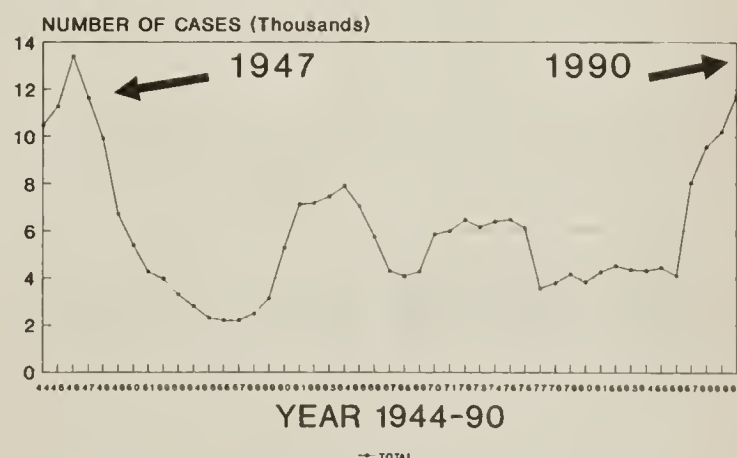
This paper reviews the epidemiology of early syphilis in New York City (NYC) between 1985 and 1990.

HISTORICAL TRENDS: 1944–1990

A review of reported early syphilis morbidity in NYC (1944–1990) indicates that current morbidity is at a level similar to that reported before the introduction of penicillin treatment (Fig 1). In 1946, 13,401 cases of early syphilis were reported.¹ In contrast, 11,750 cases of early syphilis were reported in 1990. Shortly after the introduction of penicillin for the treatment of syphilis, syphilis morbidity declined at a steady rate until the late 1950s. Since that period, morbidity trends have fluctuated.

During 1987, NYC began to experience a unexpected rise in early syphilis reports. One of the factors associated with this increase was a dramatic rise in substance

abuse, specifically crack/cocaine. This epidemic disproportionately affected lower socioeconomic groups. This phenomena resulted in increased sexual activity and exchange of sex for money or drugs.



ALL SOURCES

FIGURE 1. Early syphilis, NYC: 1944–1990.

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This paper was funded in part by funds from the Centers for Disease Control.

TABLE I. Reported Morbidity: NYC All Sources, 1985-1990*

	1985	1986	1987	1988	1989	1990	Percentage Change 1985-1986	Percentage Change 1986-1987	Percentage Change 1987-1988	Percentage Change 1988-1989	Percentage Change 1989-1990
All STDs	103,440	117,620	116,685	105,535	94,651	97,568	14	-1	-10	-10	3
P&S syphilis	2,157	2,111	4,548	5,042	4,362	4,265	-2	115	11	-13	-2
EL < 1 year syphilis	2,292	2,005	3,501	4,515	5,847	7,485	-13	75	29	30	+28
Congenital syphilis	41	33	126	356	1,017	1,051	-20	282	183	186	+3
GC	58,542	69,998	66,545	54,099	40,553	35,236	20	-5	-19	-25	-13
Chancroid	1,323	2,196	3,116	3,237	2,277	1,575	66	42	4	-30	-31

In addition, during this period, there was a shift in the population infected with early syphilis. In NYC at that time, syphilis was primarily transmitted through male-to-male contact but is now primarily a male-to-female disease. One hypothesis that may explain this shift in reported syphilis morbidity is the effects of the acquired immunodeficiency syndrome (AIDS) epidemic on sexual behavior patterns. The AIDS epidemic has caused the homosexual population to modify its sexual behavior. Human immunodeficiency virus (HIV) outreach and educational activities have been stressing safer sex techniques. These changes in behavior have decreased the risk for sexually transmitted diseases (STDs) including syphilis, among homosexual men.

SYPHILIS IN 1990

In 1990, 97,568 STDs were reported to the NYC Department of Health (DOH). The number of cases reported during CY 1990 increased 3.0% from the 94,651 cases reported in 1989. Decreases occurred in all of the major STDs with the exception of early latent (EL) syphilis under 1 year and congenital syphilis, as detailed in Table I.

EARLY SYPHILIS

According to the latest statistics reported by the Centers for Disease Control (CDC), NYC ranked first in absolute numbers of primary and secondary (P&S) syphilis cases in 1990. NYC experienced a 164% increase in early syphilis morbidity reports (P&S and EL under 1 year) between 1985 and 1990. In 1985, 4,449 early syphilis cases were reported, whereas in 1990, 11,750 early syphilis cases were reported. During 1990,

TABLE II. Comparison of National,* New York State,* and New York City P&S Syphilis Morbidity, 1986-1990

	1986	1987	1988	1989	1990
P&S syphilis					
National	25,566	30,599	35,075	44,940	48,128*
NY State	285	368	646	1,022	n.a.†
NYC	2,111	4,548	5,042	4,362	4,265
EL syphilis					
National	19,650	24,413	31,085	38,051	n.a.†
NY State	205	248	546	939	n.a.†
NYC	2,006	3,501	4,515	5,847	7,485
Congenital syphilis					
National	410	681	691	1,747	3,219*
NY State	1	3	20	76	91
NYC	33	126	356	1,017	1,051

*Provisional.

†n.a. indicates not available.

there was a 15.4% increase in the reported number of early syphilis reports relative to the number of cases reported during 1989.

One of the effects of the increase in early syphilis has been a concomitant rise in congenital syphilis. Before 1986, reported congenital syphilis morbidity in NYC remained under 60 cases per year. In 1987, the number of cases increased dramatically to 126. During 1987 and 1988, the number of reported cases increased 183% and 185%, respectively. A comparison of 1989 congenital syphilis cases (1,017) with 1990 cases (1,051) indicates a 3% increase. Table II illustrates national, state, and city reporting trends.

P&S SYPHILIS TRENDS

A comparison of 1989 and 1990 data indicates that the number of P&S syphilis cases (lesion) declined and the number of EL syphilis cases (nonlesion) increased. Lesion syphilis decreased by 2%, whereas nonlesion syphilis increased 28%. Reported cases of P&S syphilis have fluctuated erratically over the 6-year period 1985-1990 (Table III). It is difficult to discern whether the fluctuation is an accurate reflection of incidence, a result of reporting abnormalities, or a combination of both factors.

The distribution of early syphilis cases within NYC has remained stable (Fig 2). In 1987, the Borough of Brooklyn surpassed the Borough of Manhattan. Morbidity reporting from Brooklyn has remained relatively stable.

The distribution of reported P&S secondary syphilis by zip codes indicates that cases are concentrated in geographic areas in close proximity to the Bureau's seven main STD clinics.

In Manhattan, the zip codes with the highest case rates of P&S syphilis are in Harlem and Riverside. In the Bronx, the area with the highest case rates is in the South Bronx. The highest concentration of P&S syphilis cases in Brooklyn is in Bedford Stuyvesant, Bushwick, Brownsville, and East New York. In the borough of Queens, the highest case rates are in Jamaica and

TABLE III. Percentage Change in the Number of Reported P&S Cases

Year	Total
1985-1986	-2
1986-1987	+115
1987-1988	+11
1988-1989	-14
1989-1990	-2

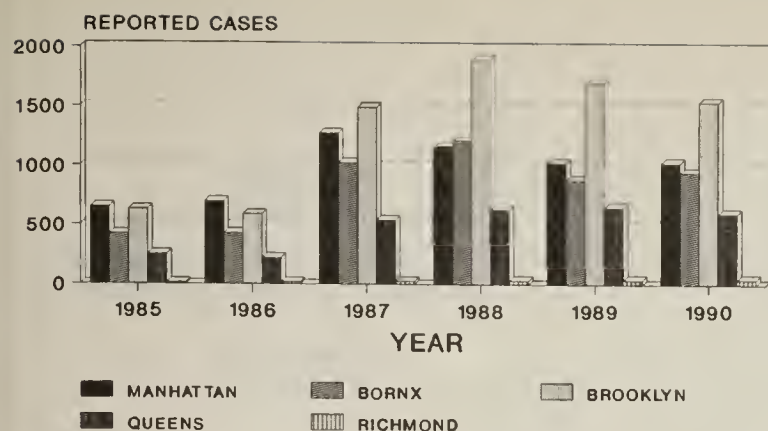


FIGURE 2. P&S syphilis reported by borough, NYC: 1985-1990.

Flushing. In Staten Island, case rates were relatively low, with the highest rates occurring in the area of St. George.

During the period 1985-1990, the age distribution of reported cases of P&S has been constant (Table IV). The mean age has been slightly higher for men than women. These data suggest that reported cases of P&S have not shifted to a younger population.

Table V indicates reported cases of lesion syphilis by sex. Whereas the percentage of cases reported for males with lesion syphilis has been consistently greater than the percentage of females, the number of males as a percentage of total reported cases has slowly decreased over the 5-year period. The data for 1990 suggest that this trend is continuing. This may be the result of several factors: homosexual males modifying sexual behavior in response to the AIDS epidemic; an increase of crack use and more females engaging in sex for the exchange of drugs; or the failure of homosexual/bisexual males to notice primary lesions and seek appropriate treatment.

During the period 1985 through 1990, the racial distribution of reported cases of P&S was relatively constant (Fig 3). Reported cases continued to be great-

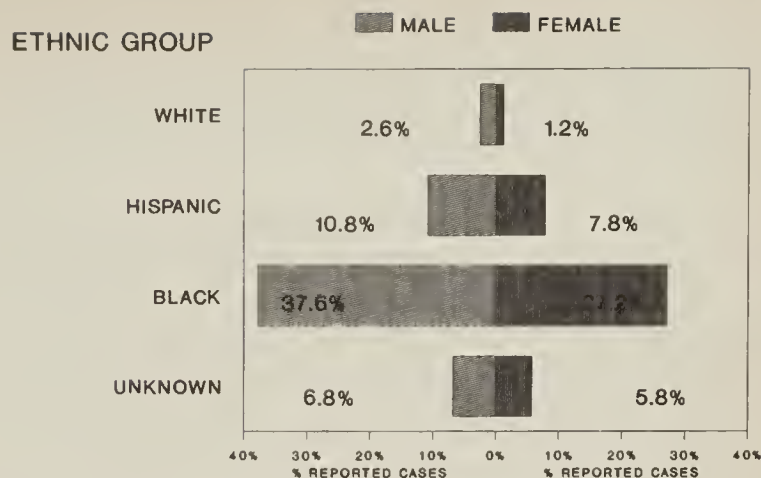


FIGURE 3. P&S syphilis by ethnic group and sex, NYC: 1990.

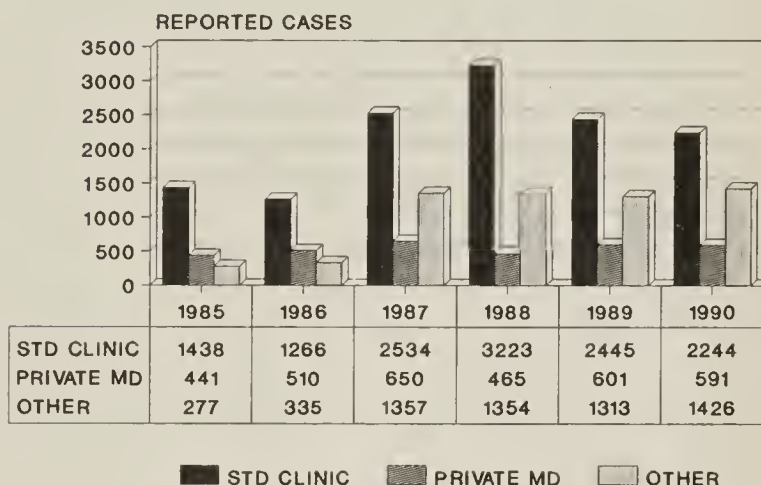


FIGURE 4. P&S syphilis by reporting source, NY: 1985-1990.

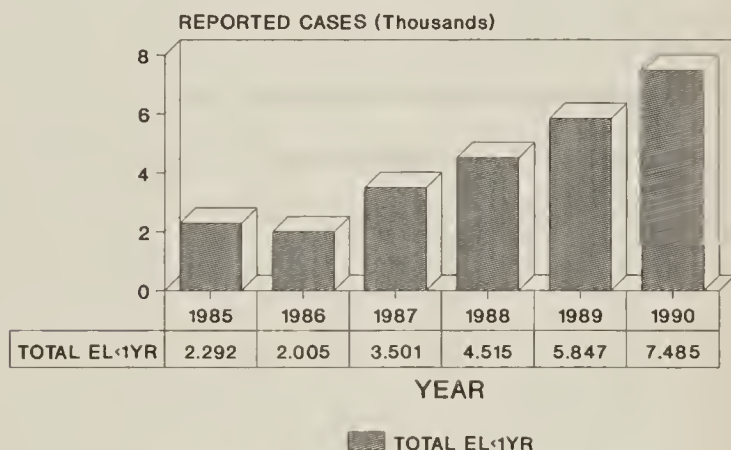
TABLE IV. P&S Syphilis, Age, and Sex Distribution Analysis

	Male Mean Age	Female Mean Age	Mean Age For Total Reported Cases
1985	31	27	30
1986	32	27	31
1987	33	28	31
1988	33	28	31
1989	34	28	32
1990	n.a.*	n.a.*	33

*n.a. indicates not available.

TABLE V. P&S Syphilis Reported to NYC by Sex, 1985-1990

	Males	Percentage	Females	Percentage	Total
1985	1,597	74	560	26	2,157
1986	1,534	73	577	27	2,111
1987	2,990	66	1,558	34	4,548
1988	3,171	63	1,871	37	5,042
1989	2,686	62	1,676	38	4,362
1990	2,476	58	1,789	42	4,265



ALL REPORTING SOURCES

FIGURE 5. EL syphilis, NYC: 1985-1990.

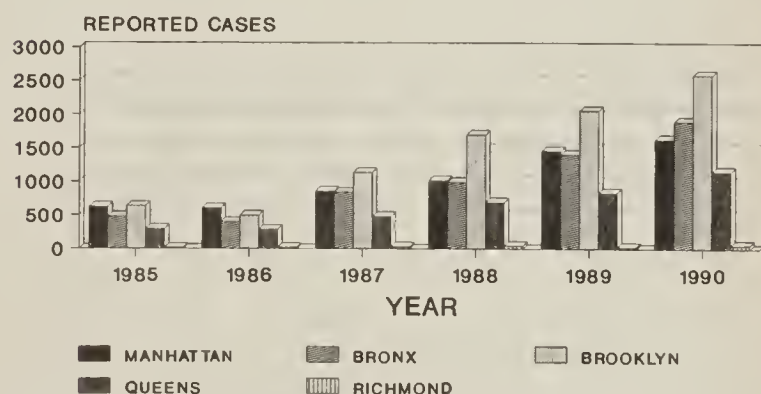


FIGURE 6. EL syphilis under one year by borough, NYC: 1985-1990.

est among the black population. During the period 1985–1990, the number of cases of P&S syphilis reported by the public sector has decreased, whereas the number of cases reported by private sources increased (Fig 4).

EL SYPHILIS TRENDS

Except for the period 1985–1986, when EL syphilis appeared to decrease, the number of EL cases has continued to climb (Fig 5). The increase in reported nonlesion syphilis in women may reflect the Bureau’s efforts to improve private sector reporting and target disease intervention activities toward women of child-bearing age. Since 1987, the number of reported EL syphilis cases has been greatest in the borough of Brooklyn, except for 1985 and 1986 when the highest number of cases were reported in Manhattan (Fig 6). The distribution of EL syphilis cases (nonlesion) closely correlates with that noted for P&S syphilis.

In Manhattan, the areas with the highest incidence are Harlem and Riverside. The South Bronx has the highest syphilis morbidity for that borough. The areas of Bedford Stuyvesant, Bushwick, Brownsville, and East New York have the highest rates of syphilis morbidity for Brooklyn. As for the Borough of Queens, the case rates are highest in Jamaica and Flushing. The Borough of Staten Island has the lowest EL case rates reported. The area in Staten Island with the highest concentration of cases is St. George. The mean age for reported EL syphilis cases remained relatively constant at 31 years of age (Table VI).

As indicated in Table VII, reported cases of EL syphilis have been increasing since 1986. The percentage of female cases has increased over the 6-year period. Currently, females make up over 57% of reported cases.

The number of reported cases of EL syphilis has been consistently highest among the black population (Fig 7). Since 1987, the percentage of cases reported for the white population has been consistent at 3%. The percentage of EL syphilis cases reported by the private sector has been increasing over the past six years (Fig 8).

TABLE VI. NYC EL Syphilis Age Distribution Analysis

Year	Mean Age
1985	31
1986	32
1987	31
1988	31
1989	31
1990	32

TABLE VII. NYC EL Syphilis Cases by Sex, 1985–1990

	Percentage		Percentage		Total
	Males	Of Total	Females	Of Total	
1985	1,370	60	922	40	2,292
1986	1,142	57	863	43	2,005
1987	1,703	49	1,798	51	3,501
1988	2,088	46	2,427	54	4,515
1989	2,316	40	3,531	60	5,847
1990	3,199	43	4,286	57	7,485

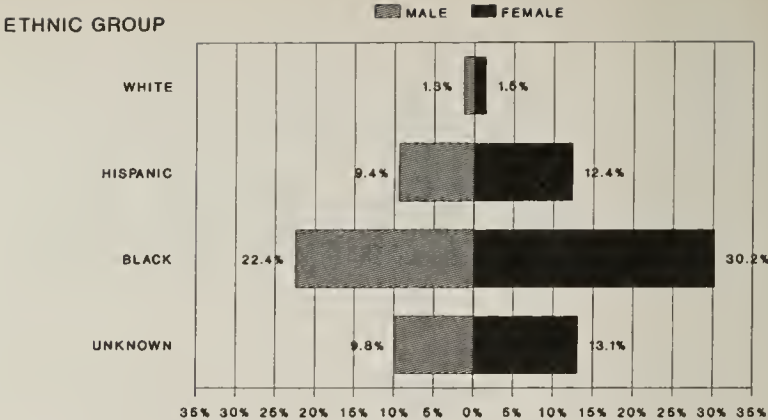


FIGURE 7. EL syphilis under one year by ethnic group and sex, NYC: 1985–1990.

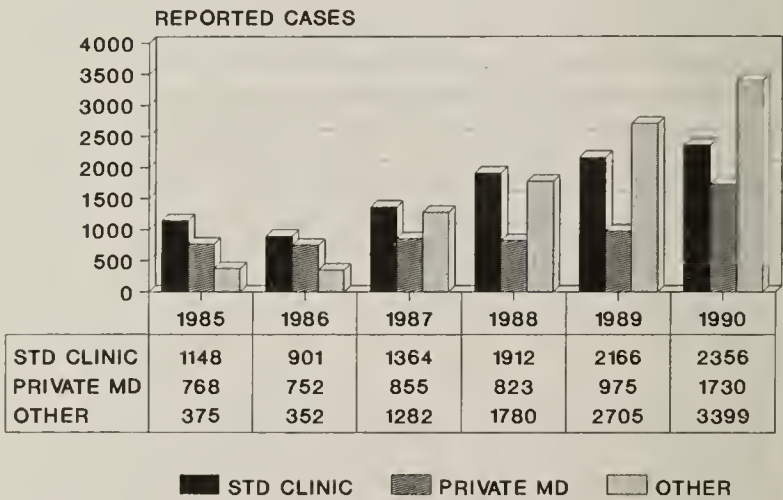


FIGURE 8. EL syphilis under one year by reporting source, NYC: 1985–1990.

SUMMARY

The resurgence of syphilis since 1986 and 1987 in NYC has been mirrored in other major urban centers nationwide.¹ Since 1988, P&S syphilis have declined, but early latent and congenital syphilis have continued to increase.

A number of features characterize this most recent epidemic:

- Starting in 1987, Brooklyn replaced Manhattan as the borough with the most number of cases of early syphilis.
- The age distribution of reported cases has remained constant.
- Women constitute a growing proportion of early syphilis, and in fact, are the majority of cases of EL syphilis. As in other parts of the nation, this may be due to diminishing risk behavior among male homosexuals and the continuing effect of the cocaine epidemic and “drugs for sex,” prostitution.²
- The black and Hispanic communities continue to be disproportionately infected. Public Health education and control efforts should continue to be focused on the communities most affected.

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New York State's syphilis initiative

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The most massive epidemic of syphilis in the post-penicillin era struck New York State in the mid-1980s. By 1990, as reported by MacCubbin et al,¹ the incidence of early syphilis in New York City and other epidemic areas far surpassed the incidence in the previous epidemic among homosexual men (1975–1985) and rivaled that in the state's greatest epidemic of syphilis, which occurred during the pre-antibiotic years after World War II.

To control this epidemic, the New York State Department of Health undertook a series of increasingly vigorous interventions, culminating in the Syphilis Initiative—an innovative, multisite screening and treatment program in New York City and seven other epidemic counties.

The Syphilis Initiative is based on the fact that the spread of syphilis is completely preventable, provided that those infected are identified and treated with penicillin or other antibiotics early in the disease process. Traditional services provided in sexually transmitted disease (STD) clinics as well as partner notification, which had controlled earlier, lesser epidemics, were not succeeding now.

The Syphilis Initiative was designed to extend the availability of screening and treatment to other sites where those infected with syphilis were likely to be encountered. The most important of these sites are emergency rooms, community health centers, family planning clinics, drug and alcohol treatment centers, jails, lockups, youth detention centers, and alternate testing sites for infection with human immunodeficiency virus (HIV).

Ongoing epidemiologic surveillance of early and congenital syphilis cases had identified the major epidemic area:

- The five boroughs of New York City
- Four nearby counties: Nassau, Suffolk, Orange, and Westchester (a fifth, Rockland, was added later)
- Two counties in northwestern New York State: Erie and Monroe, where cases were concentrated in their urban centers, Buffalo and Rochester, respectively.

PLANNING THE SYPHILIS INITIATIVE

Planning of the initiative was guided in large part by epidemiologic findings about the population at risk. By 1990, the victims of this unprecedented epidemic were primarily women (male-to-female ratio, 0.93 in New York City, 0.99 elsewhere).¹ These women were usually young and black, often drug abusers and mothers, who lived in areas characterized by poverty, inadequate educational opportunities, and inadequate health care. In many such communities, illegal drugs are readily available, but health care and prenatal care are often lacking. The current syphilis epidemic appears to have started in such communities; it certainly flourishes there.

The patients in this epidemic, regardless of gender, race, or ethnicity, tend to have other diseases associated with poverty, including HIV infection and other STDs—diseases that reflect risk behaviors that also predispose to syphilis. For this reason, reinfection of treated patients is a continuing concern. Syphilis screening and treatment of the core group was the immediate and urgent need, but a wider array of health interventions would also be needed.

These findings help to explain why persons at risk, living in these epidemic communities, are not reached efficiently by traditional epidemic-control procedures. Women coping with poverty, homelessness, drug addiction, child care, and the inherent risk of prostitution-related activities often fail to notice early symptoms, which are anatomically inapparent. Congenital syphilis frequently occurs when the mother is unaware of her own infection. In addition, persons involved with the trade of sex for drugs are unlikely to seek early care at STD clinics. When these persons are identified as syphilitic, their multiple and often anonymous sexual contacts make attempts at contact tracing difficult or futile.

New approaches were essential to control the epidemic. If individuals at high risk for syphilis did not seek screening and treatment, screening and treatment would have to seek them. The initiative therefore expanded the traditional outreach efforts to include two broad new avenues of contact:

- Sites in which people seek health care for reasons other than syphilis, but where syphilis screening and treatment can also be offered or required. Most people at risk were using these facilities, which include emergency rooms, community health cen-

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ters, family planning clinics, drug treatment centers, and AIDS/HIV alternate testing sites. Expanding services at these sites to include syphilis screening and treatment was the initiative's primary goal.

- Sites to which people are brought, not primarily for health care, but where syphilis screening and treatment can be offered or required. Typical sites of this kind are jails, lockups, youth detention centers, and alcohol detoxification sites.

These new avenues became the core of the Syphilis Initiative, which was implemented in the major epidemic areas, starting in June 1990.

IMPLEMENTING THE SYPHILIS INITIATIVE

Before the initiative was implemented, the New York State Department of Health's plans were refined in a series of statewide meetings with county government executives, county health department administrators, and the staffs of other state agencies. State and county health department staffs then visited hospitals, clinics, jails, and other sites to explain the initiative and to encourage full implementation. State staff were deployed in the targeted epidemic areas to provide training and support, monitor the activities, collect data, and evaluate the effectiveness of contact at the various sites.

In May 1990, a month before the formal start of the initiative, the Department of Health notified hospitals in the epidemic areas that testing for syphilis would be considered the standard of care for all patients seen in the emergency room or admitted for acute care. In areas marked by poverty and inadequate medical care, hospitals may be the residents' only site of contact with the health care system, often serving needs traditionally defined as primary care. Syphilis screening at hospitals, especially in emergency rooms, was expected to identify many new cases of syphilis in time for effective treatment.

In practice, a number of barriers combined to make this screening less than fully effective. Some hospitals, their staffs and budgets already stressed by the needs of their communities, found it difficult to commit adequate resources to the new testing. Various solutions were attempted, particularly to provide timely laboratory

services without cost to the facilities. Some of these solutions worked; many did not. Although the hospitals recognized the full gravity of the syphilis epidemic, they questioned whether testing of all patients was identifying sufficient numbers of new cases to warrant the staff time and costs. Studies of this issue are under way.

At all other sites, the screening and treatment activities were put in place with substantial success in all epidemic areas. These collaborative activities were implemented without legislation, regulations, or formal department directives. Industry groups collaborating in the initiative included the Hospital Association of New York State and the New York City Health and Hospitals Corporation. State agencies included the Division of Substance Abuse Services, the Division of Alcoholism and Alcohol Abuse, the Division for Youth, the Division of Parole, and the Division of Probation and Correctional Alternatives.

During the first seven months of the initiative, in the six counties outside New York City, more than 145,000 specimens were tested, with an overall reactivity rate of 2.74% (Table I). The highest rates were found in jails (5.16%) and community health centers (4.39%). Five types of facilities—hospitals, community health centers, family planning clinics, jails, and substance abuse treatment centers—each yielded positivity rates of 2% or greater in at least one county and in as many as five counties.

Not all positive reactors are new cases. Some are false positives and are excluded by confirmatory testing. Other reactors indicate residual antibodies in previously treated cases and are excluded by follow-up interviews and review of medical records. Experience to date indicates a range of new case rates among positive reactors, from a high of 50% of positive reactors in one jail in Nassau County to about 10% for aggregated specimens in some of the epidemic counties (NY State Department of Health written communication). New case rates approaching 10% would be consistent with rates found elsewhere (Personal communication, NY State Department of Health).

Further analysis of the initiative data is under way. However, the results to date appear to confirm, in the

TABLE I. New York State Syphilis Initiative, Percentage Reactive by County and Facility Type, June–December 1990*

County	Hospitals	Health Centers	Family Planning	Jails	Misc	Substance Abuse	Alternate Testing Site	Reactive	Total Tested	Percentage
Erie†	2.02	0.86	0.00	1.56	1.39	1.80	0.63	166	10,340	1.61
Monroe	1.61	—	—	2.00	—	54.5	0.97	272	16,723	1.63
Nassau	2.13	1.29	0.00	2.64	—	—	1.36	867	42,305	2.05
Orange	1.96	3.98	5.10	3.54	—	0.00	—	263	10,428	2.52
Suffolk	2.04	9.04	1.22	15.86	0.00	3.01	0.00	1,145	23,507	4.87
Westchester	2.74	2.93	—	8.92	—	—	0.58	1,262	42,021	3.00
Total								3,975	145,324	2.74
Tested	105,147	25,643	2,120	8,989	511	745	2,169			
Reactive	2,312	1,126	26	464	5	23	19			
% Reactive	2.20	4.39	1.23	5.16	0.98	3.09	0.88			

*Source: Bureau of Communicable Disease Control, May 6, 1991.

†Incomplete data.

face of New York State's massive and spreading epidemic, the importance of these new avenues of contact for syphilis screening and treatment.

WHAT NEXT IN THE SYPHILIS INITIATIVE

Given the urgency of the syphilis epidemic and mindful of delays in the nation's initial response to the AIDS epidemic in the early 1980s, the Department of Health set as the highest priority for its Syphilis Initiative a rapid start of multisite screening and treatment. Now, a year later, the time has come to address other concerns of the initiative.

Varying results for detection of new cases, which are expected on the basis of preliminary data from the epidemic counties, may provide guidance for a more narrowly focused effort, in which the selection of sites, target populations, and screening modalities is specific for each epidemic area. Data collection and analysis, which was not the highest priority early in the initiative, will be enhanced to yield the necessary information. Modifications of current activities, if needed, will be made in collaboration with personnel from the counties,

participating facilities, and others involved in the initiative.

The current epidemic is recognized as a community problem, largely rooted in the conditions of life in poor, medically underserved communities which are vulnerable to a group of related diseases. The epidemic cannot be finally brought under control without attending to the wider needs of these communities. One possible outcome of the Syphilis Initiative may be that it serves as a model for other screening and treatment programs in such communities, a model that will remain viable long after the state's devastating syphilis epidemic has abated.

Acknowledgments. The Syphilis Initiative was implemented in the field by the following staff of the Center for Community Health in the New York State Department of Health: Noel P. Bonacci, BA, Vernon Blue, BS, Al Burpee, Richard Huber, BA, R. Thomas Huntley, MA, William Hiscox, BS, James Brown, BA, and Kenneth Bomeisl, BA.

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Innovative approaches to syphilis surveillance and control in New York City: 1985-1990

KENNETH R. ONG, MD; STEVEN RUBIN; MARGARET BROME-BUNTING; KARL LABES

Several factors are responsible for the current epidemic of syphilis in the major urban centers of the United States.¹ Among these are the crack cocaine epidemic and its association with prostitution. These social determinants of the epidemic make diagnosis, contact notification, and treatment difficult. Given these factors, innovative approaches are needed to control the epidemic.

An alternative case-finding method used in Philadelphia was recently described. Health workers went to locations where crack was being used to perform on-site phlebotomy for serologic diagnosis and treatment.² For medically hard-to-reach groups, new methods such as this must be developed to go to the population most affected.

THE SURVEILLANCE LIAISON PROGRAM

The Bureau of Sexually Transmitted Diseases (STD) Control's Surveillance Unit is the recipient of all information generated as a result of the unit's activities and the reporting of medical providers and laboratories. In 1989,

through the liaison unit and other reporting sources, approximately 250,000 STD case reports or laboratory reports (presumptive of an existing STD) were received. In 1990, a total of 240,608 case reports were received by the surveillance unit. Of those, 94,446 (39%) were positive serologies for syphilis.

In 1989, 15 Public Health Advisors (PHAs) were transferred from the field to expand the Liaison unit. This was done to expedite and ensure accurate and timely reporting of sexually transmitted diseases. Members of this unit engaged in surveillance activities in 40 New York City hospitals. Toward the end of 1989, the liaison unit was reviewed, and subsequently the staff was streamlined to 11 PHAs. These PHAs concentrated their activities in 22 high morbidity medical facilities.

In 1990, the Bureau of STD Control enhanced surveillance of lower morbidity hospitals by using senior PHA staff to cover 28 additional sites. Such lower morbidity hospitals (formerly called passive hospitals) are now visited a minimum of once a month to perform laboratory log reviews/audits; to monitor the reporting of infant, adult, and cerebrospinal fluid (CSF) serologies; and to investigate cases of suspected congenital syphilis.

During the course of 1990, the number of active facilities covered by the full-time liaison staff was in-

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**TABLE I. Liaison Investigation Summary April 1990:
December 31, 1990**

Total Adult Serologies Reviewed	Total Administrative* Closure	Total Cases Previously Treated	New Identified Syphilis Cases Field [†] Follow-up
44,803	35,200 (79%)	1,215 (3%)	5,784 (13%) 2,640 (6%)

*Administrative closures are performed for serologies not meeting criteria for follow-up.

[†]Field follow-up is defined as a Public Health investigation of individuals suspected of having a sexually transmitted disease.

creased to 23 select high morbidity facilities. Currently, a total of 51 NYC facilities are monitored.

Before 1989, follow-up criteria for females with reactive serologies was limited to those females under 35 years with titers equal to or greater than 1:4.

As a result of the Bureau's growing concern regarding increased early syphilis and congenital syphilis morbidity, the criteria were revised in 1990 and are as follows:

- All females 45 and under who have a positive serology are followed in the field if they do not have a history of treated syphilis consistent with the current test result.
- All males 45 years of age and under who have a positive serology of 1:4 or greater are followed in the field, if they do not have a history of treated syphilis consistent with the current test result.

During the last three quarters of 1990, the liaison unit (with 11 PHAs) reviewed 44,803 reactive serologies from their 23 facilities. Of these, 5,748 (13%) met program criteria for follow-up and were initiated to the field. The unit also confirmed previous treatment on 1,215 (3%) reactors (Table I).

SYPHILIS TESTING AT HIV ANONYMOUS COUNSELING AND TESTING SITES

The Bureau of Acquired Immunodeficiency Syndrome (AIDS) Program Services operates nine anonymous counseling and testing (ACT) sites, which offer pre- and post-test counseling and testing services for the human immunodeficiency virus (HIV) antibody. For the year 1990, the nine ACT sites pre-test counseled 23,521 patients. Of those 23,315 (99%), specimens were drawn for the HIV antibody. Of the 23,313 patients tested for HIV, 20,838 patients (89%) were negative and 2,477 (11%) were positive. All positive HIV results were automatically serologically tested for syphilis (STS) as part of a serosurvey.

As of October 15th, 1990 all patients are offered an

TABLE II. ACT Site Patients That Signed The Consent Form To Have An STS Done

Month	11/90	12/90	1/91	Total
No. Tested for HIV	1751 (100%)	1728 (100%)	2073 (100%)	5552 (100%)
No. STS Performed	1364 (78%)	1371 (79%)	1635 (79%)	4370 (78%)
No. Declined STS	387 (22%)	357 (21%)	438 (21%)	1182 (22%)

STS. The consent form gives the Department of Health (DOH) the permission to draw this blood. To date, 80% of those patients coming into ACT sites have signed this form.

From November 1990 thru January 1991, a total of 5,552 patients were tested for HIV and 4,370 (79%) specimens were drawn for syphilis. A breakdown of the HIV/STS statistics is given in Table II. Statistics for the nine ACT sites are given in Table III. Tables IV and V summarize testing activity for the NYC and NYS ACT sites. They include routine syphilis testing activity and confirmatory testing statistics (MHATP).

THE SYPHILIS SEROLOGY EXPANSION PROGRAM

At Elmhurst Hospital, a total of 268 syphilis tests performed in January and February 1990 have been processed from the following ambulatory care sites: obstetrics, abortion clinic, infectious diseases, child-spacing, employee health service, and the Community Satellite Clinic. Twenty-seven (3.9%) of these specimens were sero-reactive. Elmhurst Hospital personnel have also begun offering STS to their emergency room patient population. The hospital administration indicated a 10% increase in serologies being performed in their emergency room during February 1990. Inpatient STS screening has increased by 5%. Additionally, Montefiore Hospital has also agreed to conduct routine syphilis testing on Emergency Room patients (15-50) years of age on the basis of the Syphilis Serology Expansion Program (SSEP) activities. Columbia Presbyterian Hospital has agreed to increase STS screening in their emergency rooms by participation in the NYC DOH SSEP.

Supported by both the NYC DOH and NYS DOH, a pilot project at the Kings County Hospital Emergency Room offered immediate rapid syphilis (stat RPR) screening and prompt treatment of targeted patients. Because of limitations of personnel, the project functioned eight hours per day (primarily in the evenings) for a duration of ten weeks. A total of 714 patients were

TABLE III. ACT Site STS Testing

	ACT I Chelsea	ACT II Bur. Labs	ACT III Ft. Greene	ACT IV Bronx	ACT V Corona	ACT VI Ft. George	ACT VII E. Harlem	ACT VIII W. Harlem	ACT IX Brownsville
No. STS	845	704	640	402	547	154	586	436	56
Pos. STS	13	5	16	16	20	5	23	9	4
% Pos.	2%	1%	3%	4%	4%	3%	4%	2%	7%

As noted, the Brownsville (ACT IX) site has the highest MHA-TP confirmed positivity rate (7%). The average positive STS rate is approximately 3%. The number of patients tested for syphilis during this period was 4,370. The number of patients that tested negative were 4,259 or 97%. Patients with positive STS: 111 (3% positivity).

TABLE IV. RPR Test Results NYS and NYC ACT Sites (Mid August–November, 1990)

Time Period	ACT Site	Number		Cumulative	
		Tested	Reactive	Tested	Reactive
End of August	N.Y.S.	434	24 (5.5%)	434	24 (5.5%)
September	NYC	n.t.*	n.t.* n.a.†	n.t.*	n.t.* n.a.†
October	NYS	422	26 (6.2%)	856	50 (5.8%)
	NYC	771	34 (4.4%)	771	34 (4.4%)
November	NYS	310	23 (7.4%)	1166	73 (6.3%)
	NYC	1406	78 (5.5%)	2177	112 (5.1%)

*n.t. indicates no testing.

†n.a. indicates not available.

screened and 41 patients were positive. A positivity rate of 5.9% was identified. With the exception of one reactor who refused treatment, all seropositive patients were treated and interviewed presumptively for syphilis, including one whose seropositive result on confirmatory testing was determined to be a biological false positive.

CORRECTIONAL FACILITIES

During the past five years the Bureau of STD Control has noticed a steady increase in both the numbers of syphilis serologies processed by NYC correctional facilities and percentage of reactive results from this population. The increase in the number of syphilis serologies processed is directly related to the increase in the number of inmates detained in NYC correctional facilities. Although a syphilis serology is a voluntary screening test, well over 99% of the inmates consent to testing. Feedback from the NYC Correctional Facility administrators also indicates that the percentage of female inmates incarcerated is also increasing. Currently, the female population represents approximately 10% of the inmate population. Data from the correctional facilities also indicate that a greater percentage of the inmates have reactive confirmatory test results (Table VI, Fig 1).

Although the current system used by the Department

TABLE V. ACT Site Syphilis Testing: August 21–December 28, 1990

	No. Tested	No. Positive RPR	Percentage Positive	No. Tested	No. Positive MHA-TP*	Percentage Positive
City	3465	174	5.5	140	54	38.6
State	1419	95	6.7	45	25	55.6
Total	4884	269	5.5	185	79	42.7

*MHATP testing on RPR positives began in November 1990.

TABLE VI. NYC Correctional Facilities Rikers Island—Montefiore Laboratory: 1985–1990

	Number of STS Processed	RPR Positive	MHATP Confirmed
1985	73,252	9,788 (13%)	5,170 (53%)
1986	91,107	10,136 (11%)	4,923 (49%)
1987	95,804	12,190 (13%)	7,289 (60%)
1988	102,345	14,745 (14%)	9,712 (66%)
1989	117,041	17,283 (15%)	12,591 (73%)
1990	113,898	16,204 (14%)	12,730 (79%)

of Corrections is successful as far as screening of inmates, there has been little success in diagnosing and treating the inmate population. Of the 42,000 inmates identified as having reactive confirmatory test results during the four years, 1987–1990, less than 2,500 (6%) were diagnosed and treated for early syphilis within the correctional system.

Because of the rapid turnover and security constraints of corrections facilities, the Bureau of Correctional Health Services has only limited success in diagnosing and treating infected individuals before release. The Bureau of STD Control deploys a liaison to ensure field follow-up whenever individuals are released without adequate documented follow-up. However, success in locating such individuals is also limited due to inadequate or incorrect locating information.

The Bureau is currently unable to determine the following: 1) what percentage of inmates testing positive were previously adequately treated and thus not requiring additional treatment, and 2) what percentage of reactive test results are repeats due to reentry into the correctional facility within the same year.

The Bureau of STD Control has proposed a project designed to provide "stat" screening and treatment to inmates found to have reactive serologies with no previous treatment. This proposal is currently under consideration with the Bureau of Correctional Health Services. Commitment on the part of the Department of Corrections and others will be required to make this project successful. This approach to rapid intervention will be pursued at other facilities with high reactivity rates and poor diagnosis and treatment indicators.

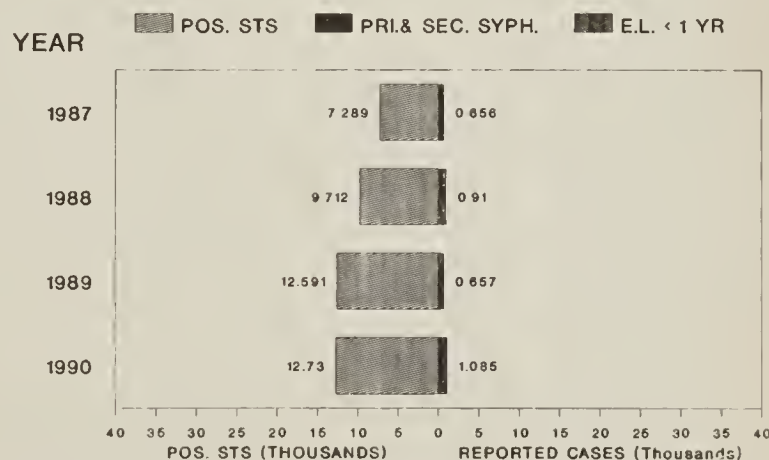


FIGURE 1. Positive STS and diagnosed early syphilis in NYC prisons, 1987–1990.

1991 GOALS

The Bureau's goals for 1991 included the following:

1. Expanding STD education and outreach activities to private medical providers, laboratories, and to high risk individuals.
2. Expanding syphilis screening to high risk individuals in targeted locations.

The Bureau of STD has developed an aggressive education/outreach protocol designed to target non-DOH providers, which are currently servicing or interacting with high risk patients. In addition, the Bureau is pursuing targeted syphilis screening activities in zip codes and/or facilities identified as high risk.

OUTREACH ACTIVITIES

During 1991, the Bureau of STD Control focused its efforts on enhancing STD education and outreach activities. The Bureau is currently targeting laboratories and medical providers in zip code areas that have the highest incidence of early adult syphilis and congenital syphilis. The Bureau is pursuing an aggressive effort to reach patients who normally do not attend STD clinics or seek STD treatment through other primary care providers. The activities scheduled are listed below.

LABORATORY VISITATIONS

There are approximately 144 laboratories located in NYC licensed by the DOH that are required to report reactive syphilis serologies to the Bureau of STD Control. During May and June 1991, the Bureau's PHA staff visited these facilities. Of the 144 laboratories located in NYC, 142 (98%) participated in this project.

The purpose of these visits was to ensure that all licensed laboratories are reporting reactive laboratory reports to the Health Department in accordance with the NYC health code. In addition, these visits fostered enhanced relationships between the DOH and private laboratory personnel by sharing disease trends and intervention strategies.

The Bureau developed a package, which was provided to laboratory personnel and which included the following: 1) an introductory letter of purpose, 2) a survey form, 3) current STD trends; 4) NYC health code, and 5) reporting forms.

With each laboratory visit the Bureau of STD controls randomly selected three reactive serology results and compared them to the Bureau's central registry to ensure reporting compliance. Of the 142 laboratories surveyed, 120 (85%) provided documentation of reactive serologies reported to the Bureau's central registry. A total of 102 (85%) of those laboratories were found to be in compliance with reporting requirements on the basis of this random sampling. The Bureau plans to follow up with those laboratories where compliance to the reporting code was not confirmed.

MEDICAL FACILITY VISITS

During the month of July 1991, the Bureau of STD Control first line supervisors visited medical providers in their catchment area identified as reporting the highest numbers of early syphilis cases. The purpose of these

visits was to educate clinicians on early adult syphilis and congenital syphilis issues/problems. In addition, there was a review of treatment guidelines and discussions concerning their reporting responsibilities as mandated per the health code. This was an important step in improving relationships between the private medical community (which is servicing an increasing number of people for STDs) and the Bureau of STD Control. To date, 25 of 30 (83.3%) medical providers were visited by the Bureau's first line supervisors. The remaining five medical facilities have been scheduled and are expected to be completed by August 1991.

COMMUNITY BASED ORGANIZATIONS

The Bureau collaborated with the Division of AIDS Program Services to provide STD education to all community based organization (CBOs) funded through the HIV Cooperative Agreement. The Bureau's education unit provided presentations to the staff of CBOs and distributed educational material for their use. The training covered the following: a) identification of the most common STDs, b) modes of disease transmission, c) risk reduction recommendations, and d) current STD trends. PHAs are responsible for follow-up consultations with the CBOs and the medical providers in these areas. The Bureau will also pursue the possibility of establishing formal referrals with those CBOs that currently do not provide medical services. To date, all of the 50 CBOs funded by CDC received an STD update presentation at their regularly scheduled monthly meetings. Additionally, 22 CBOs requested further comprehensive staff training, which has been accomplished.

INNOVATIVE SCREENING

To achieve our 1991 goals, the Bureau must strengthen its link with individuals who are not serviced by the Department of Health's STD clinics. Likewise, relationships must be established with key health care providers especially those testing and providing treatment for STDs and HIV. To accomplish this, the Bureau must return to doing several activities it routinely conducted until the mid-1980s.

In an attempt to improve our ability to identify early syphilis, the Bureau plans to use its PHA staff to conduct syphilis screening projects in non-DOH settings. These screening projects will be conducted in zip codes of the city where rates of adult primary and secondary syphilis are the highest. The Bureau anticipates access to targeted housing projects, income maintenance centers, homeless shelters and drug treatment programs. The protocol for these screening initiatives includes screening clientele on site and returning to the site within seven days with test results. Individuals with reactive results will be referred to an STD clinic for further evaluation and follow-up. Whenever possible the Bureau will also provide immediate transportation services for clients to STD clinics. The results of these initiatives will be monitored closely to ensure that they are effective and productive.

RIKERS ISLAND PILOT PROJECT

Currently, the Bureau of STD Control is collaborating with officials from the Bureau of Correctional Health Services and Montefiore Hospital to implement a rapid testing and treatment project at the Womens Detention Center, Rikers Island.

Montefiore officials have documented a 25% syphilis reactivity rate among females detained at the Rikers Island facilities. This compares with a 15% reactivity rate for STD patients. Although screening is currently accomplished through Prison Health Services personnel, the rapid turnaround makes diagnosis and treatment before release unlikely.

The STD Correction pilot project is expected to begin during the fourth quarter of 1991. A Public Health Advisor will be selected to coordinate these activities.

SYPHILIS SCREENING EXPANSION PROJECT

During the fourth quarter of 1991, the Bureau of STD will also be targeting shelters and drug treatment programs for increased syphilis screening through Bureau of STD personnel. Tentative arrangements are being pursued to include a Manhattan shelter as a participant in the bureau's syphilis screening expansion project.

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FROM THE LIBRARY

THE ETIOLOGICAL RELATIONSHIP OF SYPHILIS TO TABES AND GENERAL PARALYSIS OF THE INSANE

Byron Bramwell in his *Clinical Studies* considers this subject fully. He discusses the chief facts and arguments which were advanced in favor of the view, which he had held for many years, that syphilis is the chief factor in the production of tabes and general paralysis of the insane, and also refers to the facts and arguments which have been brought against this important view.

He quotes statistics to prove that a very large proportion of patients suffering from tabes or general paralysis of the insane have had syphilis (between 80 per cent and 94 per cent). Bramwell says that the more carefully he inquires the greater the percentage he gets. He says that seems to be the experience of all or almost all observers. As you all know, many patients whose mental powers and memories are quite normal have a delicacy in disclosing a history of syphilis both in private and hospital practice. Many patients who have had syphilis deliberately and emphatically deny that they have had the disease. So frequently is this the case that when a patient comes before him with tabes or general paralysis of the insane, he does not ask him if he had syphilis, but *when* he had syphilis. In many cases of general paralysis of the insane, memory and mental power are markedly impaired, and the statements of the patient are unreliable.

JAMES P. WARBASSE, MD
(*NY State J Med* 1906; 6:376–377)

Recommendations of the Metropolitan New York City Area Task Force on Syphilis

PASCAL JAMES IMPERATO, MD

In August 1990, Dr David Axelrod, then Commissioner of Health of New York State, established the Metropolitan New York City Area Task Force on Syphilis. The charge to this Task Force was to review the rapidly increasing problem of syphilis in New York City and the five surrounding counties, to examine the adequacy of state and local public health activities related to syphilis, and to recommend further specific actions to combat the epidemic. The Task Force consisted of 15 members and held its first meeting on September 12, 1990.

During the period of September 1990 through May 1991, the Task Force held public monthly meetings. At these meetings, the epidemiology of the current epidemic was carefully reviewed based on data presented by the technical staff of various health departments. Provider testimony was given at the meeting of November 1990, and at the December meeting, the national picture was fully reviewed with the assistance of Dr Ward Cates, Director, Division of Sexually Transmitted Diseases/Human Immunodeficiency Virus Prevention, Centers for Disease Control. At that same meeting, the relationship between syphilis, drug use, and human immunodeficiency virus (HIV) infection was fully studied.

The New York State Department of Health's (DOH) Syphilis Initiative was considered at the January 1991 meeting, along with public financing of syphilis control efforts. Syphilis in prisons, third trimester syphilis testing, and the results of a successful sero-survey for syphilis intervention in a municipal hospital emergency room were considered at the February 1991 meeting. The March 1991 meeting was devoted to syphilis control in New York City and to syphilis in the prison system. The April and May 1991 meetings were devoted to the formulation of recommendations.

On the basis of all of the detailed epidemiologic, clinical, and social data presented to it, and after having heard the testimony of a broad range of health care providers, the Task Force made the following recommendations to the New York State Department of Health in October, 1991.

A. SERVICE

1. *Screening—Health Facilities.* For counties designated by the New York State DOH, syphilis testing should be routinely implemented for all patients aged 15–45 on admission to acute care hospitals, in

emergency rooms, at ambulatory care facilities, and in other primary health care settings. The DOH should establish serologic positivity prevalence standards and should use them to determine periodically which institutions should conduct these types of testing and treatment on a routine basis and which should be exempt from them. All facilities, including exempt ones, should be periodically evaluated regarding prevalence rates.

2. *Screening—General Community.* The Task Force supports the DOH's syphilis initiative for increased community testing, treatment, and follow-up (or referral) for high-risk populations. The Task Force recommends that screening, treatment, and follow-up should occur not only in Sexually Transmitted Disease clinics and other health provider settings such as family planning centers, hospitals, emergency rooms, community health centers, and HIV testing sites, but also in drug treatment programs, jails, and detention facilities, selected state and local rehabilitation facilities, and in mental health facilities in the DOH-designated counties.
3. *Jail Facilities.* The Task Force notes that jails are important sites for identifying those with the disease. Entering prisoners may account for 20% of active cases of syphilis in the communities from which they came. Given this fact, the Task Force strongly recommends that syphilis testing be conducted on all entering prisoners within the first 24 hours, and appropriate treatment be promptly given within the first 48 hours. Correctional facilities should have a plan to ensure that prisoners with syphilis are easily accessible for follow-up within the first 72 hours. An appropriate system for repeat testing should be developed and implemented.
4. *Pregnant Women—Newborns.* Physicians and institutional providers should treat and confirm cases of syphilis among pregnant women according to the Centers for Disease Control (CDC) standards. In addition to requiring testing at the time of delivery, women must be tested during their first prenatal visit. In addition, third trimester testing is recommended for certain high-risk populations. In-

creased efforts should be made to identify exposed newborns and to treat them appropriately. Correspondingly, efforts must be continued to improve access to prenatal care for all women.

5. *Outreach.* Focused outreach activities should be undertaken at sites and in communities whose populations do not routinely use or else do not have access to health care and where the incidence of syphilis may be increased.
6. *Contact Tracing.* Increased efforts should be directed to follow-up and to the development of a range of innovative contact tracing techniques in high-risk settings and among high-risk groups.

B. EDUCATION AND TRAINING

1. *Community Education.* Educational outreach activities, emphasizing prevention and treatment, should be undertaken with a special focus on high-risk communities.
2. *Medical Schools.* Medical schools should ensure that syphilis diagnosis, prevention, and treatment are thoroughly covered at all stages of the educational process. Graduate training programs should similarly ensure that all house officers are formally taught syphilis diagnosis, prevention, and treatment.
3. *Continuing Education for Health Care Workers.* State and local departments of health should consider various methods for ensuring that all physicians who are apt to care for patients with syphilis possess adequate levels of knowledge concerning prevention, diagnosis, and treatment of the disease. Medical societies should also play a role in this effort. Correspondingly, all health care workers should possess similar levels of knowledge.
4. *Co-Infection.* Education and outreach activities for the HIV infection and the acquired immunodeficiency syndrome should also incorporate information about syphilis and other co-morbidities and vice versa.
5. *Cultural Sensitivity.* All elements of a control program should be culturally sensitive and appropriate. Training programs in cultural diversity should be given to all health care professionals involved in syphilis control programs. Efforts should be made to recruit personnel from populations at high risk for this epidemic.

C. RESEARCH—EPIDEMIOLOGY

1. *Epidemiologic Studies.* Although the epidemiologic information on the epidemic is accurate, it is incomplete. Focused epidemiologic studies should be undertaken to elucidate prevalence rates and other disease determinants among certain high-risk groups and other groups now significantly affected by the epidemic. Further recommendations or modifications of these recommendations should be made on the basis of study findings.
2. *Clinical Trials.* Prospective clinical trials should be undertaken to determine the dosage of penicillin to be administered to the infected gravida which

will be universally treponemicidal for the fetus. Prospective trials should also be undertaken to determine if one dose of benzathine penicillin is sufficient treatment for asymptomatic infected infants who have a positive serologic test for syphilis. Research efforts aimed at differentiating the truly infected asymptomatic infant from the uninfected infant who has passively acquired maternal antibody should be encouraged. The course of syphilis and its response to treatment in the setting of HIV-related immunodeficiency needs further study.

3. *Tests Development.* Priority should be given to the development of more accurate rapid tests for the diagnosis of syphilis.

D. REIMBURSEMENT—REGULATORY

1. *Testing Reimbursement.* Syphilis testing, treatment, and follow-up are an integral part of primary care. The costs associated with these components should be included in reimbursement by third-party payers. New funding sources and a reallocation of current resources will be required for these activities, which do not normally receive reimbursement. These activities are important and cost-effective since they prevent disease and will greatly reduce treatment and other costs later on.
2. *Statutory Changes.* Existing statutes and regulations should be reviewed for modifications, and new statutes or regulations should be considered to implement effectively any recommendations to combat this disease.

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THE HYPODERMIC TREATMENT OF SYPHILIS

The treatment of syphilis by means of hypodermic medication is by no means of recent origin. Hunter and Hebra are given the credit by Zeiss to have been the first to employ the hypodermic method in the treatment of syphilis. They used the bichloride of mercury, and both made the observation that syphilitic manifestations near the injection healed more quickly. In 1864 Scarenzio, of Pavia, used calomel hypodermically in the treatment of lues. He did not use the intra-muscular method that to-day is so rapidly growing in favor, but made his injection just beneath the skin. His results were not very encouraging owing to superficial abscesses and sloughing of the skin. These facts held this form of medication in disrepute for many years. It was Smirnoff, in 1882 who showed us that the formation of abscesses could be avoided by injecting the calomel suspension deep into the subcutaneous tissues at right angles to the skin by means of a long needle. Later experimenters, following the suggestion of Soffantino, a disciple of Scarenzio, have injected the mercurial salt deep into the muscular tissues where it is claimed, in an acid medium, absorption is more rapid and certain.

A short résumé of the advantages and disadvantages of the most important modes of administration of mercury in the treatment of syphilis may not be out of place. The oldest method and the one still much used is the administration by the mouth. This appeals to many a busy practitioner because of the ease with which one can write a prescription for the various preparations of mercury, either alone or in combination with potassium iodid. This should not govern us in our treatment when we have such a dread disease to deal with, the improper handling of which threatens not only the patient and the entire community, but posterity as well. The best method must be employed no matter what inconvenience it may give us. Having once acquired the technic of the intra-muscular method, we at once see the fallacy of the argument brought up by some that this method required almost the same trouble and care as a major operation.

ANDREW JAMES GILMOUR, PHB; MD
(*NY State J Med* 1908; 8:535-534)

Renal artery aneurysm in the pediatric patient

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Renal artery aneurysm, an unusual disease in the general population, is rarely diagnosed in the pediatric patient. Most pediatric renal artery aneurysms are seen in children with renovascular hypertension secondary to medial fibrodysplasia or neurofibromatosis, however, vasculitic, traumatic, and mycotic renal artery aneurysms occur as well. In general, pediatric renal artery aneurysms are clinically significant only because of the complications caused by frequently associated underlying renovascular hypertension. Large mycotic aneurysms, however, have been reported to leak or rupture. Morphologically, pediatric renal artery aneurysms have been reported as predominantly globular and irregular in shape, often situated distal to stenotic lesions or at intrarenal arterial branch points. We report a case of a smooth, saccular, pre-stenotic renal artery aneurysm occurring in a 6-month old infant with renovascular hypertension secondary to medial fibrodysplasia.

CASE REPORT

A 6-month-old male infant was admitted to the hospital with a 2-day history of fever to 105°F. The physical examination was remarkable for a blood pressure of 180/100 mm Hg, equal in all extremities. The skin was without rash or cafe-au-lait spots. The head and neck examination was notable for an injected right tympanic membrane. Examination of the heart and lungs was unremarkable. The abdomen was soft and nontender with no palpable masses and no bruits. The remainder of the examination was normal. The baby had no pertinent

medical history and was on no medications. After a negative blood culture, urine culture, and spinal tap, the child was treated for presumed otitis media. When multiple blood pressure determination remained elevated, an investigation of the patient's hypertension was undertaken.

Laboratory examination revealed a normal complete blood cell count, electrolytes, and urinalysis. The erythrocyte sedimentation rate was 17. Urinary vanillylmandelic acid, catecholamine, and metanephrine levels were all within normal limits.

The electrocardiogram demonstrated biventricular hypertrophy, and a chest radiograph revealed cardiomegaly with normal pulmonary vasculature. An echocardiogram revealed left ventricular hypertrophy, but no aortic abnormality was noted. An intravenous pyelogram demonstrated a small left kidney (Fig 1), a finding which was confirmed by ultrasonography. Digital subtraction angiography with a selective left renal arteriogram (Fig 2) showed a 0.5–0.8 cm smooth saccular aneurysm arising from the inferior portion of the main renal artery approximately 0.5 cm from its origin, with delayed flow distally. The remainder of the abdominal aorta was normal. Selective renin values were obtained: the left renal vein renin was 29.87 ng/mL/hr and the right was 14.67 ng/mL/hr; the value above the renal veins was 29.31 ng/mL/hr and below was 25.69 ng/mL/hr.

Renal ultrasound and abdominal computed tomography (CT) showed no renal or adrenal masses. Magnetic resonance imaging (MRI) of the head did not reveal any intracranial masses or aneurysms.



FIGURE 1. Intravenous pyelogram demonstrating a small left kidney.

The infant's blood pressure was poorly controlled on triple agent therapy using propranolol, enalapril, and hydrochlorothiazide. Surgical exploration was undertaken in the hope of performing a left renal revascularization procedure. At surgery, the kidney was noted to be smooth, unscarred, and extremely small. The left renal artery was cleared proximally to its junction with the aorta. A smooth saccular aneurysm was observed about 0.5 cm distal to the junction of the left renal artery and the aorta. Because of the small size of the left kidney, a nephrectomy, rather than the planned revascularization, was performed. Pathologic examination of the specimen showed medial fibrodysplasia of the left main renal artery with stenosis (Fig 3). The kidney parenchyma and intrarenal vasculature were normal. Since the surgery, the patient has been normotensive and on no medications.

DISCUSSION

Renal artery aneurysms in the general population constitute only 1% of all aneurysmal disease.¹ The incidence of the disease depends on the patient population studied. In autopsy stud-



FIGURE 2. Selective left renal angiogram demonstrates a smooth saccular aneurysm just distal to the ostium of the left renal artery.

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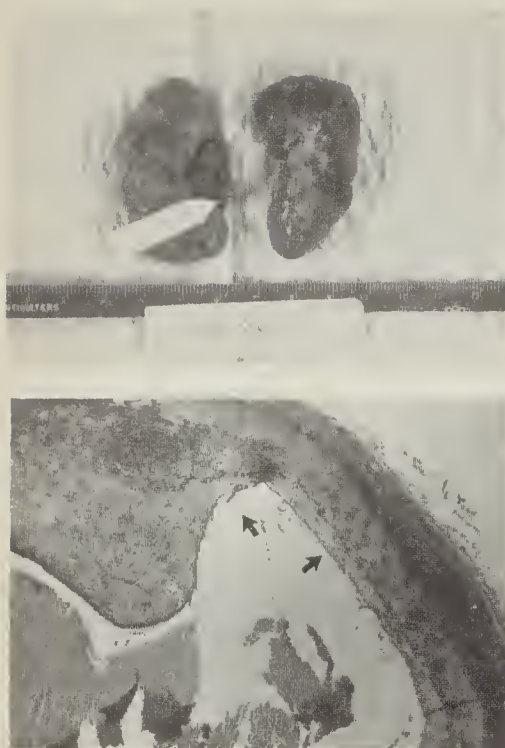


FIGURE 3. Top, the resected specimen demonstrating a small left kidney with renal artery aneurysm (white arrow). Bottom, microscopic section of the aneurysm showing thinning and fragmentation of the medial elastic lamina.

ies, the incidence has been reported to be 0.01% to 0.015%;¹ however, in patients undergoing arteriograms for non-renal disease, it was reported to be as high as 0.1%.²

Renal artery aneurysm in the pediatric age group remains an exceedingly rare entity. The true incidence is hard to determine, since the great majority of pediatric renal artery aneurysms are discovered incidentally during the work-up of suspected renovascular hypertension. In this subgroup of patients, the incidence of aneurysms is low; approximately 5%–10% of children with renovascular hypertension have renal occlusive disease.^{3–5} In one series of 853 children evaluated for elevated blood pressure, only 27 (3%) had hypertension secondary to renal artery stenosis. Of these, only two patients demonstrated a renal artery aneurysm by angiography.⁵ In Stanley's series of 44 pediatric patients operated on for renovascular hypertension, six renal artery aneurysms were encountered.⁴ There are rare case reports of renal artery aneurysms in children who were normotensive, but these have almost exclusively been mycotic or vasculitic in origin.^{6–8}

The pathologic basis of pediatric renal artery aneurysms is distinct from that of the adult type. In adults, the majority of aneurysms are saccular in morphology and occur at primary or secondary renal artery bifurcations.

They fall into two distinct categories. One group comprises those aneurysms presumed secondary to medial arterial wall degeneration and elastic lamina fragmentation. The second group includes those aneurysms complicated by atheromatous changes; whether these changes are primary or secondary is not known. The majority of adult aneurysms are not associated with renal artery stenosis. Medial fibrodysplasia with intervening macroaneurysms, such as those commonly affecting adult women, are not associated with renal artery stenosis and are not seen in children.⁴ The pathology of aneurysms secondary to the arteritides (polyarteritis nodosa, Kawasaki's disease, Takayasu's arteritis) or of infectious origins (mycotic aneurysms) is no different in the adult or child.

In children, most renal artery aneurysms are associated with medial fibrodysplasia or neurofibromatosis with accompanying renal artery stenosis. The underlying defect seems to be an atypical intimal and medial-perimedial fibrodysplasia of the arterial wall with loss of smooth muscle and fragmentation of elastic tissue, leading to narrowing of the arterial lumen and renin-mediated systemic hypertension. Stanley has classified these stenoses according to morphology. Smooth concentric or eccentric ostial stenoses account for 50% of the affected patients, usually those with neurofibromatosis or with congenital abdominal aortic developmental anomalies. Mid-renal focal or long tubular stenoses account for another 20% of children with renovascular hypertension and are usually accompanied by intimal proliferation. Isolated segmental stenoses comprise another 20% of hypertensive patients.⁹

It is within this latter group of pediatric patients with renovascular hypertension that renal artery aneurysms are seen. They occur after stenoses or at bifurcation points⁴ and have been thought to be attributable to post-stenotic flow disturbances. They are more globular and irregular in appearance than those seen in adults. Pediatric renal artery aneurysms located intrarenally at single or multiple sites of arterial branching are less common than aneurysms of the main renal artery or its external branches.¹⁰

In this case, the renal artery aneurysm was smooth and saccular in morphology in contrast to the usual globular, irregular type and was located proximal to the stenotic area. As with

most other renal artery aneurysms in children, congenital medial fibrodysplasia caused renal artery obstruction and documented renovascular hypertension in this patient. Although post-stenotic dilatation was not a factor in the pathogenesis of this aneurysm, it is likely that an arterial wall defect secondary to fibrodysplasia contributed to its formation.

The treatment of renal artery aneurysms in children must be approached in the context of the underlying process involved. In cases of vasculitic or mycotic aneurysms, the most serious complication is aneurysmal rupture. Some of these aneurysms have been reported to regress spontaneously or with treatment of the underlying disease process.^{5,7,11,12} Where the underlying process is medial fibrodysplasia causing stenosis and associated renovascular hypertension, nephrectomy had been the mainstay of therapy. However, percutaneous transluminal angioplasty,¹³ transcatheter renal artery embolization,^{10,14} and aortorenal bypass using saphenous vein or hypogastric artery grafts^{16–18} have increasingly replaced nephrectomy as the treatment of choice. In this patient, revascularization was not done because of the small size of the affected kidney, even though it should have been technically feasible.

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Isolated iliac artery aneurysm

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Aneurysms of the iliac arteries most commonly occur in conjunction with abdominal aortic aneurysms. Isolated aneurysms of the iliac arteries, on the other hand, are uncommon.¹ Although the first report of successful treatment of an iliac artery aneurysm was by Valentine Mott in 1827,² only occasional reports have appeared in the current literature.

CASE REPORT

An 86-year-old man was admitted to the hospital with the complaints of dyspnea and anterior chest pain radiating to both shoulders. He had never had these pains before and had no significant earlier medical or surgical history.

His blood pressure was 120/80 mm Hg; pulse, 100/min; respirations, 24/min; and temperature, 98.4°F. Examination of the heart revealed a regular rate and rhythm with a non-radiating II/VI systolic ejection murmur at the apex. The abdomen was soft and non-tender, with no palpable masses and a reducible inguinal hernia. The extremities were without edema. The dorsalis pedis and posterior tibialis pulses were 1+/4+ bilaterally. Serum electrolyte levels were normal, but the hemoglobin was 7.7 mg/dL, and the hematocrit was 25.1%. The white blood cell count was 5,300/mm³. Cardiac enzymes were not elevated. The electrocardiogram was remarkable for slight ST elevations in leads II, III, and AVF. The patient received a transfusion of one unit of packed red cells, and the pain resolved without elevations of the cardiac enzymes.

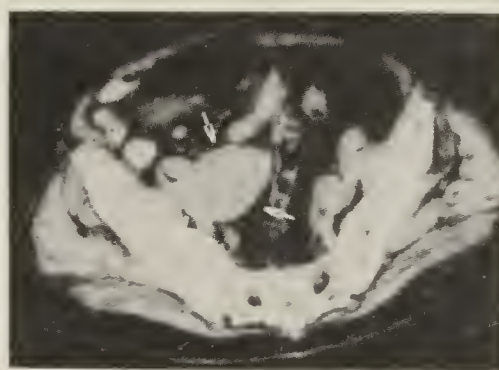


FIGURE 1. CT scan with intravenous contrast demonstrating a 6-cm right common iliac artery aneurysm. It was found to be located in the external iliac artery at surgery.

On the third hospital day, the patient had right lower quadrant pain without guarding or rigidity. The hernia was partially reducible and non-tender. Abdominal radiographs showed air in the colon without signs of obstruction. Computed tomography (CT) (Fig 1) demonstrated a right common iliac artery aneurysm, which was 6 cm in diameter.

The patient was taken to the operating room and found to have an aneurysm not of the right common iliac artery, but of the right external iliac artery; it was 7 cm in greatest diameter with no evidence of prior leakage. The aneurysm was resected using a Dacron graft with an end-to-end proximal and end-to-side distal anastomosis to the right external iliac artery. A 10-cm leiomyoma was found in the jejunum and was resected; the hernia was also repaired. The postoperative course was complicated by respiratory failure, and extubation was not performed until the 15th day after surgery. Thereafter, recovery was unremarkable.

DISCUSSION

Isolated aneurysms of the iliac artery are rare entities, comprising less than 1% of all arteriosclerotic aneurysms.¹ Lucke and Rea,³ in their study of 12,000 autopsies, found only one

aneurysm of the iliac system while identifying 432 aneurysms of the abdominal or thoracic aorta. A similar incidence has been found by others.⁴⁻⁷ Richardson and Greenfield⁸ recently reviewed 72 cases of iliac artery aneurysms and found only 18 to be isolated aneurysms. It is interesting to note that none of these isolated aneurysms occurred in the external iliac artery. Six occurred in the common iliac artery, and the remainder occurred in the internal iliac artery. Why the external iliac artery is so rarely the site of an isolated aneurysm is unclear. The natural history of such lesions is of progressive enlargement at a rate of 4 mm per year with eventual rupture, usually within five months of diagnosis.^{1,7,9,10} This carries a mortality rate of 50%-75%.^{1,7,8,11}

Iliac artery aneurysms are usually asymptomatic until they reach a large size or rupture. The most common presenting symptoms include pain in the pelvis, back, or lower extremity, or are related to the gastrointestinal or genitourinary tracts.^{1, 11-13} Symptoms arise as the result of progressive enlargement of the aneurysm or from the inflammatory reaction associated with it, leading to displacement of pelvic organs and compression of adjacent structures.^{8,11} Patients may complain of urinary urgency, hesitancy, nocturia, or even pulsatile micturition.^{1,11,14} Less commonly, they complain of flank pain mimicking renal colic or have anuria.^{1,11,14,15} Sciatica and ipsilateral neurologic deficits have also been described, resulting from the aneurysm herniating through the sciatic notch and compressing the sciatic nerve.^{1,16} Unilateral or bilateral lower extremity edema may also occur as a result of

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compression of the femoral or iliac veins.¹ Physical findings are usually present only when the aneurysm has attained a very large diameter, being palpable in only 20% of cases.^{14,17}

The average diameter of unruptured iliac aneurysms is 8.5 cm,^{1,7} whereas that of ruptured aneurysms is reported to be 5.4 cm.^{8,14,18} This may be the result of the indolent and asymptomatic nature of these aneurysms.

As demonstrated by the discrepancy between the CT scan findings of a 6-cm aneurysm of the right common iliac artery the the intra-operative findings of a 7-cm aneurysm of the external iliac artery, it can be seen that the CT scan is not always sufficient in the work-up of an iliac artery aneurysm.⁹ An arteriogram should be considered as a supplement to the CT scan, especially if the aneurysm appears to be located on an internal iliac artery and may be ligated.¹¹ Angiographic confirmation of the patency of the opposite internal iliac artery would help determine if ligation of the aneurysm would be safe. Whether an arteriogram should be performed before all elective repairs depends on the preference of the surgeon, but it should be done if any doubt remains as to the nature of the aneurysm.

Rupture is associated with sudden and severe pain in the lower back, abdomen, inguinal region, testes, and the medial aspect of the thigh. The physical examination may reveal ipsilateral neurologic deficits or vascular compromise.^{1,11,14} A scrotal and peri-

anal hematoma, although not always present, is highly suggestive of a ruptured iliac aneurysm.^{7,11} The emergent nature of these lesions, even when asymptomatic, becomes apparent when one notes the diameter of a normal iliac artery to be less than 1 cm. In 19%–23% of patients, the aneurysms will be bilateral.^{1,3–7}

The treatment of choice for aneurysms of the common and external iliac arteries is aneurysmorrhaphy with graft interposition,^{1,14} although simple ligation may be adequate for aneurysms of the internal iliac artery.^{1,7,11,19–21} Mortality rates for elective repair range from 10%–20%.^{1,7,8,11} Rupture and emergency resection carries a mortality rate of 50%–75%.^{1,7,8,11} In light of these data, elective repair should be recommended for all but the smallest iliac artery aneurysms. Management without surgery may be considered for isolated iliac aneurysms less than 3 cm in diameter. However, these aneurysms should be followed closely with serial CT studies.^{7–9} For those patients who are poor surgical risks, embolization of an internal iliac artery aneurysm may be considered.²²

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Left renal artery dissection caused by a football injury

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Football is popular in the United States on both the amateur and professional level. With an increasing number of participants, the injuries associated with the playing of football have also increased.^{1,2} Heightened awareness of sports-related abdominal injuries in

individuals injured while playing football will improve the chances of rapid diagnosis and appropriate treatment. We present here a case of a “recreational” football player who sustained a serious injury to his left flank and left renal artery, which resulted in the loss of his left kidney.

CASE REPORT

A 36-year-old male, “recreational” football player was playing a game of tackle

football without appropriate protective equipment. While running with the football, he was tackled on his left side and fell to the ground. As he arose, he experienced severe pain in the left flank. He attempted to continue playing, but the pain became very intense and he was rushed to a nearby community hospital.

Physical examination revealed a well-developed male in acute distress complaining of severe left back pain. His blood pressure was 140/90 mm Hg; pulse, 106/min; and he was afebrile. On auscultation,

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FIGURE 1. Renal scan demonstrates non-perfused left kidney, possibly consistent with left renal artery occlusion (reverse "L" side).

good breath sounds were present bilaterally. His abdominal examination was within normal limits. He had left costovertebral angle tenderness on percussion. No ecchymosis or hematoma was seen in the lumbar paravertebral region. The neurologic examination was normal.

Laboratory results, including a complete blood count, and determinations of serum electrolytes, blood-urea-nitrogen, and serum amylase were all within normal limits. However, urinalysis was significant for a large number of red blood cells. A renal scan (6 mci of ^{99m}Tc pentetic acid) was obtained to determine if he had sustained a renal contusion. Sequential imaging at 5, 10, 15, and 25 minutes demonstrated persistent absence of tracer activity in the left kidney, possibly consistent with left renal artery occlusion (Fig 1). The renal scan was completed four hours after the injury and two hours after arriving in the hospital emergency room.

A computed tomography (CT) scan of the abdomen was obtained to delineate better the injured left renal and para-renal tissues. The CT scan revealed non-perfusion of the left renal artery and vein, with hematoma in the left renal pelvis (Fig 2). The remaining intraperitoneal organs were unremarkable.

Seven hours after the injury, he was evacuated via helicopter to the University of Maryland Medical System for an emergency aortogram. He was rapidly transported to the angiography suite where the aortogram was performed. The aortogram demonstrated complete occlusion of the

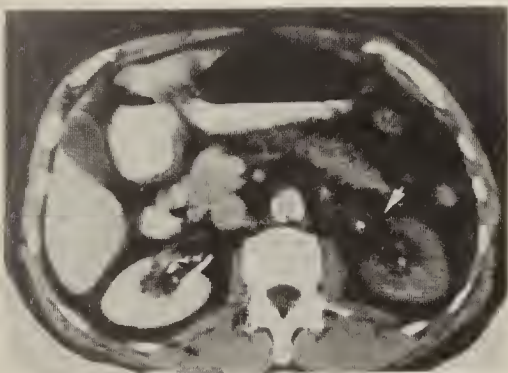


FIGURE 2. CT scan demonstrates non-perfusion of the left renal artery and vein with hematoma in the left renal pelvis (arrow).



FIGURE 3. Aortogram demonstrates complete occlusion of the left renal artery with no collateral circulation (arrow).

left renal artery with no collateral (accessory renal artery) circulation to the left kidney (Fig 3). After the aortogram, he was immediately taken to the operating room (ten hours after the injury), where celiotomy revealed an infarcted left kidney with disrupted veins in the left renal pelvis and a hematoma. A left nephrectomy was performed. He had an uncomplicated postoperative course and was discharged from the hospital on the seventh day after surgery. Pathologic examination revealed an intimal dissection of the left renal artery with thrombus.

DISCUSSION

The vast majority of studies of football injuries have concentrated on high school, college, and professional football players.¹⁻¹¹ Shields and Zomar⁹ reported the injury incidence in one professional football team during a six-year period from 1973 to 1978. A total of 2,139 injuries occurred in 222 players during all preseason, regular season, and playoff games. Most of the injuries (88.5%) required no physician follow-up, and players were able to return to the game or practice field. Of all injuries, 2% required a hospital stay, and slightly more than 1% required surgery. These injuries occurred in spite of appropriate protective equipment, training techniques, training personnel, coaching, medical screening, and excellent playing surfaces. The highest incidence of injury was to the knee.

Recent studies by Halpern and Thompson et al^{1,2} have identified risk factors associated with increased incidence of injury: these include age (older players have higher injury rates); previous season injury; helmet type (padded vs suspension); and make of shoulder pads. In general, the authors

found that sprains and strains accounted for about 40% of injuries; contusions, 35%; fractures, 10%; concussions, 5%; dislocations, 5%; and other (unspecified), 15% of all injuries. Again, the single most common anatomical location for injury in these football players was the knee, in spite of the wearing of appropriate padding and soccer-style shoes. It is not surprising therefore that more serious injuries occur in "recreational" players who do not have any of the previously mentioned advantages.

Of all reported abdominal injuries, 10% resulted from participation in sports, according to Diamond.¹⁰ Among team activities, most injuries occurred in contact sports such as football, rugby, soccer, and wrestling.

Players with blunt abdominal trauma usually present with pain. Pain usually begins immediately after receiving a blow, but it may occur insidiously after a blow or some hours after an athletic event. The spleen is the most commonly injured organ, followed by the liver and the kidney.

Diamond found that renal injuries from direct blows were particularly common in football and rugby players. He recommends that athletes with gross blood in the urine should be evaluated in a hospital. In the absence of shock, an expanding hematoma in the flank, or extravasation of urine as seen on an intravenous contrast CT scan, most of these patients can be managed without surgery.¹⁰

In 1988, 17 players died while playing football (seven more than in 1987).¹¹ Only one death was due to abdominal trauma that resulted in a ruptured spleen.

Renal artery dissection caused by blunt trauma is a rare vascular disorder,^{12,13} resulting in renal infarction in most cases if the diagnosis is not immediately suspected. The diagnostic procedure of choice is an emergency arteriogram. However, the diagnosis of renal artery dissection caused by blunt abdominal trauma is very rare, and most patients with hematuria will have a renal contusion. Therefore, an intravenous contrast CT scan should be obtained quickly.¹⁰ The CT scan will demonstrate decreased perfusion to the kidney with compromise of its arterial circulation. In addition, the CT scan can rule out additional retroperitoneal or intra-abdominal injuries (especially to the contralateral kidney). The renal arteriogram should be obtained after the CT scan demon-

strates decreased perfusion to the kidney to document the cause of the arterial compromise (intimal dissection vs thrombus) and the extent of the occlusion. If arteriography is not available at one hospital, then the patient should be stabilized, hydrated intravenously, and immediately transferred to a medical center with the capability of performing an emergency arteriogram. Precious time should not be wasted on a renal scan.

If the diagnosis of renal artery dissection is confirmed on arteriography, the patient should be operated on immediately.¹⁴ If the kidney is still viable, all attempts at renal revascularization should be performed.¹³ If the kidney is infarcted, then a nephrec-

tomy should be performed (preserving the adrenal gland) to remove the traumatized kidney.¹⁵

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FROM THE LIBRARY

ENGLISH AND AMERICAN FOOTBALL STATISTICS

We have long since become inured to the innuendoes and slurring comparisons which reach us from the United Kingdom, holding up to us as they do the well-nigh ideal state of affairs existing in football conditions there. We have become accustomed to regard the game a thing of beauty as played upon its native Anglo-Saxon soil. Not only has the skill of play been developed to a marvelous degree, but the percentage of fatalities and even injuries have, we are repeatedly assured, been restricted to an enviably small figure. The essential nature of the participants—to say nothing of their up-bringing—is itself of such a character as to preclude the possibility of brutality in the game. All of which we accept in good part. It may be, however, that we have all this while allowed ourselves to be regaled by a too rosy picture, for now the *Lancet*, of November 16th, reports that this year's crop of casualties in England to date includes six deaths and sixty disablements from football. This seems to be doing pretty well for a beginning, inasmuch as the English football season does not close until the end of March. Some few things may be said in our favor still.

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(*NY State J Med* 1908; 8:34)

Address correspondence to Editor, New York State Journal of Medicine, 420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication after editorial review. All letters are personally acknowledged by the Editor.

Neural network programming

TO THE EDITOR: As members of the Neural Net Group at the New York State Psychiatric Institute, we welcomed the appearance in the *Journal* of the article by Brandsetter et al on neural network programming.¹ Psychiatrists^{2,3} and neurologists⁴ have shown early interest in neural network modeling.

With input of vague, dirty, and incomplete data, neural networks have shown improved ability to make complex evaluations, even clinical ones, as compared with standard statistical computations and rule-based programs, and even with human practitioners.⁵ Neural networks may solve problems in surprising ways, and new features discriminating the data may emerge, much in the way a creative human may look at data in a new way.

Neural networks are not so opaque to comprehension as black boxes, but they require experts to retrieve and interpret their decisions. Perhaps someday they will need psychiatrists to help them. One of us (Dr Forrest) has suggested that with differing parameters of function, neural networks can resemble various human characteristics. Although the valuations their connections arrive at are open to inspection, the pattern thereby comprised may not be intuitively obvious to a human, and parts of the problem may need to be resubmitted to a network to break out the solution process.

Any physician interested in neuromental function would profit by learning about neural networks through widely available courses and books.^{6,7} Neural nets are something new under the sun that go beyond conventional artificial intelligence in their promise and can be made to evolve. As models of mind and brain, particularly in very human functions such as language and face recognition,

neural networks will make very good mental furniture and even company.

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Confusing labeling of food products

TO THE EDITOR: Allergy to peanut is a well-recognized clinical problem among allergists and those who have experienced a serious and recognized reaction. This allergy is known to affect many children and adults,¹ is usually not outgrown,² and results in anaphylactic reactions.³ Yunginger et al cite the cases of five individuals ages 11, 16, 18, 19, and 43 who accidentally ingested minimal portions of peanut-containing foods with resultant anaphylaxis and death.

In spite of this, there is at least one candy manufacturer which produces two candies and labels one as clearly containing peanut and the second, which looks identical, as "Plain." The obvious implication to the average individual is that one product contains

peanut and the other product does not. Both products contain peanut. This was brought to our attention by observing a severe allergic reaction in a peanut sensitive-child after the ingestion of the "Plain" candy.

In very small print on the package there is mention of peanut as one of the ingredients. While this points out the constant need for food allergy patients and others to read all labels very carefully for even minimal food content, it should also serve as a warning to food manufacturers to avoid misleading labeling of foods.

The manufacturer of the candy in question, when contacted about this problem, replied that only a very small amount of peanut was used in the plain candy. They seemed to miss the point that just this small amount of peanut is enough to produce a violent allergic reaction in certain sensitive individuals. The company further stated that current labeling laws do not require them to list minute amounts of peanut as an ingredient and that they did so voluntarily so that consumers, if they would read the label, would know that peanut was one of the ingredients in the candy.

Another example of confusing labeling is a non-dairy creamer. The obvious implication here again is that the food is free of milk and milk products. However, when one reads the fine print, it indicates that it does contain casein, a milk sub-fraction. The ingestion of this food by violently milk-sensitive patients could result in at least a speedy trip to the local emergency room and possibly a fatal anaphylactic reaction.

In view of this type of information, we urge that physicians and the Food and Drug Administration move to seek better labeling requirements. We hope that food manufacturers would refrain from adding potential allergens as minor ingredients to candies or foods unless very clearly stated. It certainly would save parents, patients,

physicians, and local emergency rooms a great deal of stress.

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The right to leave a hospital against medical advice

TO THE EDITOR: The vast majority of hospitalized patients leave the hospital after a physician discharge order. A small percentage of patients, however, sign out against medical advice (AMA).

At the time the patient decides to leave AMA, some explanation is ordinarily provided to the patient which summarizes the adverse consequences of this action. In addition to the adverse medical outcome, we have observed a phenomenon which goes beyond health consequences. We have noted in several hospitals over several years time a common practice in which nurses inform patients choosing to leave AMA that they may incur financial responsibility as a result. Specifically, the patients are told that insurance companies may not pay for their hospital stay if they sign out AMA.

The four most common third party payors (Medicare, two private insurance carriers, and an HMO) were

contacted with regard to their policy concerning reimbursement for patients leaving AMA. They all responded that payment for the hospitalization would be unaffected by such action, and specifically, that there would be no adverse financial impact on the beneficiary (patient).

Signing out AMA is simply a withdrawal of consent to be hospitalized, which all competent patients voluntarily give at admission. As such, leaving AMA is a specific instance of the larger concept of refusal of treatment. Competent adults have the right to refuse treatment unconditionally and without explanation. Specifically, however, this principle is ordinarily coupled with the requirement to provide adequate information. In this context, refusal of treatment is in reality, part of the doctrine of informed consent.

Informed consent is given most attention with regard to surgical treatments, but is presumed if not actually identified as such, in all medical treatment relationships. Inpatient hospitalization represents an intensive medical interaction. It is institutionalization during which the patient's daily activities are strictly regimented. Diet and activity are prescribed by the physician and enforced by the nursing staff. In addition to having the activities of daily living controlled, the patient is subjected to a variety of invasive and non-invasive testing, usually with little or no advance notice. Health care professionals, however, should not lose sight of the voluntary nature of hospitalization.

It is within this context that the concept of signing out AMA must be viewed. The scant reference in the literature to AMA discharge reflects the popular notion that this represents a "compliance" problem, often related to substance abuse.¹ Patients who leave the hospital AMA are made to feel they are "breaking the rules," and are usually subjected to intense pressures to stay in the hospital. Sometimes this may be justified since the patient may be quite ill. Many times, however, this is not the case,

and patients can often go home with little or no risk.

The doctrine of informed consent is an important one. It would seem to have a particularly important place in the setting of hospitalization where personal liberty is curtailed. Leaving the hospital AMA is often a consequence of poor communications regarding medical conditions and the goals of treatment. It has been recognized that threats to sign out AMA are often a means to communicate a feeling of fear or anger when earlier verbal or behavioral messages were ignored.^{2,3} A related explanation is the desperate attempt to assert some control in a situation in which the patient feels helpless and vulnerable.⁴

Understandably, most health professionals believe it is in the patient's best interests to remain in the hospital in most AMA encounters. Furthermore, they have a professional obligation to advise patients of the medical reasons for this belief. Resorting to financial threats, however, is particularly coercive to a patient already in a vulnerable state.

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WINTER SPORTS MEDICINE

By Murray Joseph Casey, MD, Carl Foster, MD, and Edward G. Hixson, MD. 425 pp, illustrated. Philadelphia, PA, FA Davis Co Publishers, 1990. \$65.00 (hardcover)

This is a multidisciplinary reference text for the primary care physician interested in winter sports. The authors (coaches, athletes, physicians, physiologists, nutritionists, kinesiologists, biomechanical engineers, equipment experts, and psychologists) epitomize and highlight the importance of an organized collaborative team effort. They are recognized authorities in their respective fields and many are accomplished athletes in a winter sport.

In spite of the fact that winter sports became a reality in the United States and the Olympics only in the early part of this century, the knowledge base of this field has exploded in only the last 20 years. The book is divided into six parts: general; medical problems; injuries; skating; skiing and sliding; and climbing, trekking, and winter camping. There are 45 individual chapters spread over the six parts. Topics cover preparation; training; nutrition; team physician responsibilities; drugs and doping; youth and women; sports psychology; infectious diseases; headaches; dermatologic problems; hypothermia; exercise-induced bronchospasm; head, eye, and maxillofacial injuries; biomechanics; physiology and pathophysiology of skating; skiing and sliding; climbing, trekking and camping, and hillside evacuation techniques.

Comparable texts in this interesting field are conspicuously absent. Rather a number of physiology and clinical sports texts have sections in them devoted to this particular topic. *Wilderness Medicine* by Auerbach et al comes closest to addressing the issues covered in the present volume.

Although the text is full of important facts, there are a number that this reviewer found most enlightening. Injury rates for ski jumpers, speed skaters, sledgers, and lugers are remarkably low considering the risk factors (eg, height and speeds). For instance, no fatalities have been recorded for the bobsled and luge since

1976! Although rates for alpine skiers are comparable, the overall number of injuries is much higher since there are some 10 million participants in this country alone. In addition like many other sports, the inexperienced beginner sustains more injuries, whereas the experienced downhill devotee sustains more serious trauma. Females actually have a higher incidence of lower extremity injury than their male counterparts. In spite of the sophisticated technological aspects of ski bindings that now spare injury to the ankle and tibia, the anterior cruciate is still vulnerable.

From a physiologic perspective, one learns that the aerobic capacity of speed skaters is actually less than their roller skating, cycling, or running counterparts. The highest VO_{2max} belongs to cross country skiers who are generally larger than runners and more efficiently and evenly distribute work throughout their body muscle mass.

Hockey produces the highest injury rates and most severe trauma. In spite of the significant decline of eye and facial trauma due to the use of facial protectors and helmets, severe spinal cord injuries are still unacceptably high, and the incidence of injury rises dramatically as one progresses from amateur to professional status. Surprisingly, goalies have the lowest incidence of injuries.

Prevention is critical for trekkers and climbers. A proper diet (60%–70% carbohydrates) and ample fluids go far toward reducing the incidence and severity of mountain sickness. Adequate acclimatization (1,000 feet/1 day) mitigates the changes of serious pathology (high-altitude pulmonary edema), high-altitude cerebral edema, and high-altitude cachexia. The “death zone” of over 17,000 feet represents the altitude above which acclimatization cannot keep up with hypoxic deterioration.

Several minor areas of this book could be improved. These include the need for a discussion (table/graph) of the wind-chill factor in hypothermia, dosage of certain medications (ie, acetazolamide and antibiotics), expansion of the team physician chapter to include more generic management protocols (ie, what happens when a player goes down on the ice?), and

consideration of both the negative (ie, failure to perform and loss of self-esteem) and positive (ie, improved self-confidence) psychological aspects of sports participation, particularly in children and adolescents.

These suggestions aside, *Winter Sports Medicine* is a welcome addition to the library of sports medicine physicians. It reflects team collaboration among a wide variety of experts collected for the express purpose of promoting the safety, enjoyment, and performance of athletes involved in winter sports.

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HISTORY OF VASCULAR SURGERY

Edited by Steven G. Friedman, MD, 212 pp, illustrated. Mount Kisco, NY, Futura Publishing Company, 1989. \$27.50 (hardcover)

Dr Steven Friedman has gone to considerable trouble to document a history of vascular surgery from antiquity to modern times. In doing so, according to Dr James A. DeWeese, who wrote the forward to the book, Dr Friedman read over 90% of the original or translated articles in his bibliography and interviewed over 25 contemporary vascular surgeons. Since his history starts from approximately 700 BC with Sushruta's description of how to control hemorrhage and ends 207 pages later with a brief description of percutaneous transluminal angioplasty, one can appreciate the fact that the presentations of the accomplishments of various luminaries in the field of vascular surgery through the years is succinct and intended to pique one's interest in further reading when, in the word of the author, one “catches the fever.”

Since there is no volume that attempts to cover the history of the entire field of vascular surgery, Dr Friedman's book fills a void which hopefully will attract other similar volumes in greater detail. He is assistant professor of clinical surgery at North Shore University Hospital in Manhasset, New York, and Cornell University Medical College. He served a vascular fellowship at New York University Medical Center, and has

done a prodigious amount of investigative work that has resulted in what appears to be an authoritative enumeration of the contributions of a number of vascular investigators through the ages.

The volume is profusely illustrated. It relies heavily on "firsts" and emphasizes the "daring and abandon" of individuals such as Ashley Cooper, said to have ligated an aortic aneurysm with his patient in a hospital bed, well before the advent of antisepsis, blood and food replacement, or anesthesia. The questions that probably can never be answered relate to the motivation that drove many of these pioneers to their heights of accomplishment and daring.

There are few volumes that relate to the history of vascular surgery and none that attempt to match the scope of this one. It would perhaps be valuable in future volumes to include some of the primary original publications, at least in part, but in some instances in toto, so that one can begin to appreciate the thought processes experienced by these great surgeons.

The volume serves as an acceptable introduction to the history of vascular surgery and should stimulate those so inclined to seek additional information, the bibliography serving as a useful guideline for further reading.

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CARDIOVASCULAR PHARMACOLOGY

Third Edition. Edited by Michael J. Antonaccio, PhD, 572 pp, illustrated. New York, NY, Raven Press, 1990. \$75.00 (hardcover)

Cardiovascular pharmacology is a rapidly changing field, as evidenced by the extensively revised third edition of this book written for students and researchers of the subject. The volume is multi-authored, consisting of 12 detailed reviews covering cardiovascular physiology, pathophysiology, neuropharmacology, and clinical syndromes. Dr Antonaccio has edited these separate contributions into a cohesive textbook with almost no redundancy or overlap. The contributing authors are respected pharmacologists and clinicians from academic institutions and the pharmaceutical industry. The

book is logically arranged with the initial chapters devoted to the more basic aspects of cardiovascular pharmacology. Subsequent chapters discuss in detail the mechanisms of action of adrenergic agents, calcium blockers, vasodilators, ACE inhibitors, and the effects of central neurotransmitters. The last five chapters are more clinically oriented, covering pharmacologic interventions for heart failure, myocardial ischemia, hyperlipidemia, arrhythmias and antiplatelet, anti-thrombotic and anticoagulant therapy. The writing and tables are clear, especially in the more clinically oriented chapters. Figures are used to explain successfully more complicated subjects and concepts.

Although written for those who need a working knowledge of the detailed molecular pharmacology in this field, there is ample useful material for the practitioner. Chapters on lipid agents, thrombosis and antiarrhythmic agents are especially well organized and presented, with individual agents discussed within the context of their class, and relevant clinical information summarized at the end of each section. Finding pertinent material in these chapters is quick and satisfying. Lists of adverse effects and interactions are provided in summary form in these chapters. The book's use as a reference source is enhanced by a comprehensive and useful index. However, clinical information such as recommended doses and alternate dosage forms (long-acting formulations and topical administration) are ignored, and differences between agents in a particular class of agents are dealt with in a cursory fashion.

Factual matter is accurate and contradictory statements (such as about the clinical use of calcium antagonists) reflect honest differences of opinion. Topics covered represent the leading edge of cardiovascular pharmacology research; however, some clinically important drugs are given little evaluation. Thrombolytics and class IC antiarrhythmics are controversial in clinical practice at this time, and a solid review of the pharmacologic facts concerning these would have been helpful. A helpful chapter on diuretics has been deleted from the previous edition and not replaced. These shortcomings are minor, and deal only with the utility of the book to the clinician. Overall this book is solidly conceived, written, edited, and constructed (with heavy paper to withstand frequent use).

The intended audience of cardiovascular researchers will be very satisfied with the book, especially with the extensive reference lists of almost 3,000 citations. These represent both primary studies and relevant reviews of material that could not be adequately covered within the scope of this publication. Practitioners who want a better understanding of drug actions will find this book informative and readable. Those who require a book on cardiovascular therapeutics will be better served by others, cheaper handbooks which are available. However, for a detailed understanding of mechanisms of action, this book is not equaled by any other available text in coverage or value, and will be extremely useful.

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CARDIAC CATHETERIZATION, ANGIOGRAPHY, AND INTERVENTION

Fourth Edition. Edited by William Grossman, MD, and Donald S. Baim, MD, 698 pp, illustrated. Malvern, PA, Lea & Febiger, 1991. \$59.50 (hardcover)

Since the first edition in 1974, this text, now co-authored with Donald S. Baim, MD, has become the standard reference in diagnostic and interventional catheterization. This edition maintains a similar basic organization to the previous editions, with sections on theoretical and practical considerations in the performance of cardiac catheterization and angiography, diagnostic interventions and special catheter techniques, current interventional techniques, and a final section on clinical/hemodynamic/angiographic profiles of specific clinical entities.

As in earlier editions, this structure has served the reader well. The provision of both a detailed analysis of the methodology used in assessing hemodynamic disorders and the presentation of specific cases with complete analysis in the last section provides a very concrete approach. This is particularly useful for both the student learning the field and the more experienced catheterizer reviewing areas less commonly used.

Consonant with the evolution of invasive cardiology. There is now a new section on interventional techniques. Included in this is a chapter on

coronary angioplasty, as in the earlier edition. However, there is now an expanded section on laser therapies, and new sections on devices (eg, stents and atherectomy), balloon valvuloplasty, and pediatric interventions.

The chapters on the techniques of cardiac catheterization are very elegant, direct, and provide virtually "hands on" descriptions of the techniques. The chapter on pressure measurement is a uniquely detailed and informative one of the features and limitations inherent in this basic and universally used aspect of catheterization. The chapter on the calculation of valve areas has been updated to reflect newer studies on the relationship between flow, pressure gradients, and actual valve area (eg, including a section on flow dependence of valve area calculations). The section on coronary angiography has similarly been expanded, in particular with discussions of saphenous vein bypass graft and internal mammary artery cannulations. This reflects the increasing number of patients requiring recatheterization after the widespread use of coronary bypass surgery over the past two decades.

The chapter on cardiopulmonary support has been expanded from that of intra-aortic balloon counterpulsation to include other forms of percutaneous cardiac support, including percutaneous bypass and left ventricular assist devices. Similarly, the section on coronary angioplasty has been expanded to include coronary angioplasty of bypass grafts, patients with unstable angina, and patients with acute myocardial infarction.

This Fourth Edition, therefore, remains as with all previous editions, an outstanding resource for all physicians in cardiology, invasive or not, with its clinical sections in many ways superior to those of the comprehensive textbooks in cardiology. The updated sections meet the current needs of the invasive cardiologist, and the traditional sections continue to provide a resource for the methodologies we all take too much for granted, and for answering questions about less commonly encountered clinical and hemodynamic problems. It is a superb work that should be on each cardiologist's bookshelf.

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VIRAL INFECTIONS OF HUMANS: EPIDEMIOLOGY AND CONTROL

Edited by Alfred S. Evans, MD, 829 pages, illustrated. New York, Plenum Publishing Corporation, 1989. \$75.00 (hardcover)

Although only 109 pages longer than its last edition, the third edition of *Viral Infections of Humans: Epidemiology and Control* adds considerably more information to each of its updated chapters. New chapters on Hantavirus, retroviruses, and hepatocellular carcinoma have been added. The text described all the important and some of the more unusual causes of human viral disease. It is comprehensive, extremely well organized, and written with an international scope and flavor. Evans is associated with the WHO Serum Reference Bank, Section of International Epidemiology, and is on one faculty of the Department of the Epidemiology and Public Health at the Yale University School of Medicine. Thirty-six other contributors represent the fields of virology, epidemiology, clinical medicine and pediatrics nationwide and worldwide.

The text, consisting of 30 chapters, is divided into three sections. These sections are "Introduction and Concepts," "Acute Viral Infections," and "Malignant and Chronic Neurological Diseases Associated with Viruses." Each chapter is divided into three sections and subsections, making the text easy to read to both a superb study and reference work. Descriptive epidemiology (incidence and prevalence, epidemic behavior, geographic, temporal, age, sex, race, and occupational risks), epidemiologic methodology (including laboratory methods), and mechanisms and routes of transmission are clearly described for each viral agent. Each chapter discusses clinical syndromes, host responses and immunity, prevention, treatment, and control. The chapter on retroviruses is well written, but the statistical tables from 1987 and 1988 only sadden the reader when one compares these data with present reports and realizes how swiftly the AIDS epidemic is spreading. Rapid diagnostic test methods, the use of DNA probes and ELISA testing are described, although polymerase chain reaction is not. Some of the most interesting writing comes at the beginning and end of each chapter where

the authors describe the history of each disease and unresolved problems or questions. The text is well illustrated with black and white diagrams, charts, maps, and photomicrographs. There is one color print of an immunofluorescence stain, but unfortunately, there are no clinical macrophotographs. Each chapter is thoroughly referenced and importantly, includes a list of suggested readings.

The first two chapters of the text, "Epidemiologic Concepts and Methods" and "Surveillance and Seroepidemiology," expertly explain both basic and complex concepts that bring the entire field of viral study into focus. The discussion of proof of causation, comparing Koch's postulates with those of Rivers and immunologic proof should clarify once and for all viral diagnosis for the clinician. Evans goes on to discuss problems and advances in the control of viral diseases in both developed and developing countries.

Methods of disease surveillance for both developed and developing countries and a brief discussion of basic epidemiologic methods make this readable text an excellent one volume work for students, practitioners, and public health professionals in any part of the world. The text teaches virology and is at the same time a valuable source book on the subject.

A major related work is *Field Virology* (Second Edition by Fields BN, Knipe DM, Chanock RM, et al; Raven Press, New York, 1990) which is nearly 2,400 pages long, well illustrated, and encyclopedic in its scope. It is an excellent text but more intended as a library reference than the handier work edited by Evans.

In sum, the third edition of *Viral Infections of Humans: Epidemiology and Control* is a necessary addition to any infectious diseases library and mandatory reading for anyone interested in understanding human virology.

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COCAINE IN THE BRAIN

Edited by Nora D. Volkow, MD, and Alan C. Swann, MD, 250 pp, illustrated. New Brunswick, NJ, Rutgers

University Press, 1990. \$40.00 (hardcover)

The current cocaine epidemic in America has renewed interest in this fascinating and unique drug. Much has been written on cocaine and its effects on the cardiovascular system. Until recently, few data existed on cocaine in the brain in spite of the fact that cocaine abuse has been associated with neurological and psychiatric symptoms. Psychiatric symptoms related to cocaine abuse range from depression to psychosis. Cocaine's effects on the brain range from mild agitation to seizures, convulsions, and death. The drug has also been associated with cerebral ischemia, infarction, hemorrhage, vasculitis, and stroke.

This is a timely and scholarly publication. There is no topic of greater concern to the public and the medical profession than cocaine abuse. *Cocaine in the Brain* consists of eight chapters followed by adequate current references. In general, the chapters are presented in an interesting and understandable fashion. Introductory chapters on history, epidemiology, and trends of stimulant use are included, providing adequate background information for the reader to understand and appreciate the subject matter.

The book focuses on the effects of cocaine in the human brain, its interaction with neurotransmitters, glucose metabolism, and cerebral blood flow. Experimental studies have shown that maximal concentration of ^{11}C -cocaine occurs in the caudate and putamen regions probably reflecting the binding of cocaine to a dopamine transporter. The evaluation of regional brain function, neurotransmitters and receptors in chronic cocaine abusers by various imaging techniques, including positron-emission tomographic (PET) scan, is discussed in detail. As a research tool, the PET scan may provide a way of establishing the link between the biological actions of cocaine and its behavioral effect in the brain.

The chapters are written by some of this country's leading experts on cocaine abuse who achieve their stated objectives. The only minor criticism of this work is that the references at the end of the chapters are not numbered but instead arranged by authors' names. This book is a must on the reading list of all who work in the field of chemical dependency and/or substance abuse. It should be a valuable

reference to all health professionals interested in cocaine abuse.

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ETHICS CONSULTATION IN HEALTH CARE

Edited by John C. Fletcher, PhD, Norman Quist, and Albert R. Jonsen, PhD. 209 pp. Ann Arbor, MI, Health Administration Press, 1989. \$24.00 (hardcover)

This is a timely and useful volume for hospital administrators and members of hospital ethics committees. Moral dilemmas in the clinical setting seem to be growing in both volume and complexity. Many hospitals now use ethics consultants to assist in addressing these issues more sensitively and intelligently. Sometimes these are individuals detached from the institution (academic philosophers in medical ethics), and at other times they are clinicians who are members of the institutional ethics committee. In either case, there is no credentialing process for ethics consultants. There are no board-certified ethics consultants. No doubt some enthusiastic educational entrepreneur could invent a credentialing process, but that assumes that we already know what the role of an ethics consultant ought to be, when in fact this is a highly problematic issue.

This volume is divided into four parts. The three essays in the first part address the problem of defining the role of the ethics consultant. The Ackerman essay is the most analytic of the three. He identifies several critical moral conflicts in the role itself. Are ethics consultants simply supposed to help with analyzing clinical moral problems or are they supposed to provide "correct" moral solutions? Are ethics consultants supposed to be advocates for the interests of the patients, or are they supposed to remain impartial among conflicting interests? Are ethics consultants simply there for moral reflection, or do they have an obligation to "blow the whistle" on attending physicians who ignore the advice of consultants and choose courses of action consultants judge morally objectionable, and what are consultants supposed to do when existing hospital policy would require a course of action that consultants

judge morally objectionable? That is, must consultants accept existing institutional rules as a limiting framework?

In Part Two, there are again three essays that examine the practical role of an ethics consultant in the hospital. The Fletcher/Boverman essay describes the actual evolution of the role of the ethics consultant at one medical center. The Purtilo essay examines four possible models of the consultant role, starting with clinical consultation in medicine and going to the mode of consultation characteristic of clinical psychiatrists. However, in my judgment the most insightful, down-to-earth essay is by James Drane, "Hiring a Hospital Ethicist." Among a wealth of practical insights Drane discusses seven characteristics a hospital administrator would not want in an ethics consultant, namely, someone who was too theoretical, dogmatic, obsessive/compulsive (insisting on doing "the" right thing immediately in a complex organization instead of muddling through toward a workable compromise), too directive, too aggressive, too paternalistic, too literalistic. His conclusion is that a good hospital ethicist "must be sensitive to the peculiarities of a clinical setting and respectful of persons with extensive clinical experience." This sounds easy and obvious, but as a philosopher, I know how easy it is to impose academic analytic rigor in clinical circumstances where such rigor is simply inappropriate.

Part Three is comprised of two essays that discuss the problem of the value biases of the consultant. The issue here is whether consultants can monitor their own biases; and, if not, whether institutions can do so effectively. Although this might be enough of a problem, it is made more complex by an issue Jonsen raises in his essay, namely, whether an ethics consult should be part of the standard of care in certain clinical situations.

In Part Four, John Robertson examines the scope and grounds of the legal duties and privileges of ethics consultants. This is a path-breaking essay in that there is only now beginning to emerge a discussion of these issues. The concluding essay by John Fletcher discusses standards for evaluating an ethics consultation.

The essays in this volume are uniformly clear and well written. Taken together, they delineate very nicely a broad range of legal, ethical, and organizational issues and options that

must be considered by hospital administrators in creating an ethics consultation service. Cases are used generously to give the discussion a concrete focus. Overall, this is a volume administrators should find useful and insightful.

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TREATING STRESS IN FAMILIES

Edited by Charles R. Figley, PhD. 352 pp, illustrated. New York, Brunner/Mazel Publisher, 1989. \$35.00 (hardcover)

As the latest volume in the Brunner/Mazel series on psychosocial stress, *Treating Stress in Families* promised to provide a comprehensive overview of the field of family stress management and an opportunity for the clinician to learn more about how to intervene effectively with families whose coping skills are overtaxed by stressful life events. As such, I eagerly approached reading this book as an important resource.

Edited by Dr Charles Figley, who has written extensively on psychosocial stress, most notably on post-traumatic stress disorder and its effect on Vietnam veterans, the book is a compilation of chapters by a number of experienced clinicians and educators. Its format is divided into three sections: "Theoretical Orientations," "Treatment Approaches," and "Treating Specific Family Stressors."

In Section One on "Theoretical Orientations," McCubbin and McCubbin begin by presenting a very thorough summary of the family stress literature that is nicely followed by Everett Worthington's chapter on "Matching Family Treatment to Family Stressors." Here an outline is

provided as to how different treatment modalities can be more or less effective depending on family style and differing family life stressors. Taken together, these two chapters present a very clear and concise framework for the book as a whole, and successfully stimulate the reader's interest to continue to read on.

Having completed this section, I anticipated learning more about specific treatment approaches which are successful in helping families manage stress. My hopes were only partly met; the chapters in this section are divided to include overviews of various treatment orientations, including family systems, cognitive behavior therapy, rapid strategic intervention, and psychoeducational approaches. Although this material can benefit those unfamiliar with these approaches by providing a sense of how each approach can be used in specific situations, the scope is very broad and less useful in providing new information for experienced clinicians. In addition, the presentations are somewhat uneven. The chapters on family systems and cognitive behavior were organized in a manner that provides little sense of the process of treatment. Although following the same format, the chapters on "The Rapid Strategic Intervention Approach" and "A Psychoeducational Approach" are more successful in summarizing the key points of these two methods, and I would recommend both as good introductory reading.

Dr Fraser's chapter is particularly useful for professionals who seek information on brief treatment interventions. In this respect, it was the best chapter in this section.

Section Three, on working with specific family stressors, provides uniform brief descriptions of the problems of child sexual abuse, adolescent drug abuse, parent/adolescent conflict, and rape and ways of effectively working with families experiencing these problems.

Each chapter also includes a fairly thorough bibliography enabling interested readers to learn more about these specific topics. I would like to have seen included in this section more discussion of how to intervene in a broader range of crises encountered by families, particularly around issues of mid-life and later life stages, and some mention of how to help families confronting medical illness. Perhaps we can look forward to this in a future volume.

In his introduction to the book, Dr Figley states his hopes and that of the contributors that this book serve as an "important resource to practicing clinicians, and that it will be adopted as a textbook for courses and training programs in the area of stress and the family in departments of psychology, counseling psychology, nursing, social work, psychiatry, family medicine, child development, and family studies." Although I am not familiar with all of the literature available on this topic, this appears to be overly ambitious. What the book is successful in providing is an interesting and informative service review of the topic and of the variety of intervention techniques available to help families cope with stress. The reader can then move on to explore more detailed and specific resources.

In this same manner, it can be useful to family practitioners and other primary care providers who encounter similar situations in working with families in their office practice. As such, it is a welcome addition to the medical literature.

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AIDS

Productive Living Strategies for People with AIDS. Edited by Jerry A. Johnson. 227 pp. Binghamton, NY, Haworth Press, Inc, 1990. \$29.95 (hardcover)

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ton, NY, Haworth Press, 1991. \$24.95 (hardcover)

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Fundamentals of Multi-system Trauma Care. Parts I and II. 30 minutes. Westlake, Ohio, Glacier View Medical Education, 1991. Two week rental \$45.00, Purchase Price: \$250.00.

Assessment and Triage. 28 minutes. Westlake, Ohio, Glacier View Medical Education, 1991. Two week rental, \$195.00 purchase price.

Pediatric Emergencies. 25 minutes. Westlake, Ohio, Glacier View Medical Education, 1991. Two week rental, \$45.00, \$195.00 purchase price.

Medical Emergencies. 27 minutes. Westlake, Ohio, Glacier View Medical Education, 1991. Two week rental, \$45.00, \$195.00 purchase price.

Pilot study assesses prostate cancer screening methods in general practice setting

A prostate cancer screening program is aimed at detecting malignant lesions before they have spread beyond the prostate. At this stage of disease, radical prostatectomy can produce a cure. As prostate cancer is the most common cancer among men, the potential for increasing survival rates and reducing the need for costly long-term treatment has fueled the search for effective screening techniques.

Initial studies by the American Cancer Study suggest a screening regimen that includes digital rectal examination (DRE), transrectal ultrasound (TRUS), and the prostate-specific antigen (PSA) assay (see NEWS BRIEFS, *New York State Journal of Medicine* 1991; 91: 379). Chadwick et al have applied these three methods in a pilot screening program incorporating their general medical practice, and they report their results in a recent issue of the *Lancet* (1991; 338:613-616).

Eight hundred and fourteen men aged 55-69 years were targeted for the program. Within the one-year study time, 671 (82%) of these men came to the office for a variety of reasons; 472 (58%) agreed to undergo a general health check. Of these 472 patients who comprised the screening group, 407 (86%) underwent DRE, and 437 (93%) had PSA measurements. Seventy-five men who had either an abnormal prostate on palpation or a PSA level greater than 4 ng/mL were referred for TRUS; 68 of these men underwent the procedure, and 29 had biopsies of suspicious lesions. Seven patients (1.7% of those screened) were found to have prostate cancer. Further testing revealed that the cancer was confined to the prostate in all seven men.

All of the patients found to have prostate cancer had increased PSA levels, whereas only one of these patients had abnormal findings on DRE. The authors contend that this study suggests an "apparent lack of value of the digital examination in our study," and they question the value of DRE as a screening tool, at least when performed by general practitioners, who may be less experienced at detecting prostatic abnormalities on palpation than would urologists. Because rectal examination "adds to the time and cost of the screening process" and is, according to the findings of this study, less appealing to patients, the authors suggest that perhaps, "prostate specific antigen alone should be used in future studies."

Lyme disease and infected ticks are spreading throughout New York State

Reported cases of confirmed Lyme disease in New York State have increased from 106 in 1981 to 1,471 in 1988, and 1,942 in 1989 (*JAMA* 1991; 266:1230-1236). Likewise, Lyme disease-related hospital discharges in the state rose from five in 1982 to 1,043 in 1989. In New York State, Lyme disease became legally reportable in 1986.

The original four counties endemic for Lyme disease were Suffolk, Nassau, Westchester, and Putnam, all located in the southeastern region of the state. Since 1986, disease activity has expanded to the north and west of these counties, and as of 1989, there were eight endemic counties—the original four and Rockland, Dutchess, Orange, and Ulster. The vast majority of cases still originate in the four previous endemic regions.

Surveillance activities of *Ixodes dammini*, the tick vector, and *Borrelia burgdorferi*, the causative agent of Lyme disease, reveal that "dispersion of ticks has occurred in parallel with the expansion of the range of reported human cases of Lyme disease," with human disease following the presence of ticks in a previously nonendemic area by at least one year. "These findings suggest that this epidemic may continue to grow both in number of cases and in geographic areas considered at risk for Lyme disease acquisition." To avoid underreporting and misdiagnosis of this potentially treatable disease, the authors of this article recommend public health efforts to educate patients and physicians on the causes, symptoms, testing, diagnosis, treatment, and prevention of Lyme disease, even in nonendemic areas.

Rapid creatine kinase-MB assay helps identify victims of myocardial infarction

To institute appropriate treatment as quickly as possible, emergency room physicians need to ascertain whether patients that seek emergency care for a range of clinical symptoms have suffered a possible myocardial infarction. Laboratory studies of creatine kinase levels had previously been too slow and cumbersome to be of use in an emergency room setting. A quantitative, rapid creatine kinase assay recently approved by the Food and Drug Administration, is simple to perform and is appropriate for use in the emergency room by specially trained, nonlaboratory personnel (*Ann Emerg Med* 1991; 20:954-960).

Although negative results with the rapid assay do not rule out a myocardial infarction, a positive result with a sensitivity of 100% may identify victims of myocardial infarction who would otherwise be discharged or excluded from coronary care units.

In the study population of 271 patients seen in the emergency room for various symptoms potentially associated with myocardial infarction, the rapid assay was positive for 32 patients, using excess sera from initial laboratory tests. Sixteen of these patients had been admitted to the intensive care unit, three to monitored ward beds, eight to unmonitored beds, and five were discharged. Further enzyme studies revealed that all three patients in monitored beds and five of the eight patients in unmonitored beds had evidence of myocardial infarction. "These 'misdiagnosed' patients have been shown to have a higher mortality than those admitted to coronary care units," suggesting a useful role for this rapid enzymatic assay.

George Downey Anderson, MD, Mount McGregor. Died September 12, 1991; age 73. Dr Anderson was a 1946 graduate of New York Medical College. He was a Diplomate of the American Board of Obstetrics and Gynecology and a Fellow of the American College of Obstetricians and Gynecologist. He was a member of the Pan American Medical Association, the Medical Society of the County of Saratoga, and the Medical Society of the State of New York.

John M. Astrachan, MD, New York. Died July 4, 1991; age 63. Dr Astrachan was a 1953 graduate of New York Medical College. He was a Diplomate of the American Board of Psychiatry and Neurology and a Fellow of the American College of Obstetricians and Gynecologist. He was a member of the American Psychiatric Association, the New York County Medical Society, and the Medical Society of the State of New York.

Maurice Bruce Bangel, MD, Great Neck. Died May 21, 1991; age 89. Dr Bangel was a 1925 graduate of Virginia Commonwealth University, Medical College of Virginia School of Medicine, Richmond, Virginia. He was a Fellow of the American College of Gastroenterology and a Qualified Fellow of the International College of Surgeons. His memberships included the New York State Surgical Society, the American College of Occupational Medicine, the American Geriatrics Society, the American Society of Abdominal Surgeons, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Donald M. Brough, MD, Irvington. Died February 2, 1991; age 65. Dr Brough was a 1948 graduate of the University of St Andrews School of Medicine, Dundee, Scotland. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the New York Academy of Medicine, the American Psychiatric Association, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

William Bruce Carter, MD, Watertown. Died August 30, 1991; age 71. Dr Carter was a 1944 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Surgery, a Diplomate of the American Board of Neurological Surgery, and a Fellow of the American College of Surgeons. He was a member of the American Association of Neurological Surgeons, Medical Society of the County of Jefferson, and the Medical Society of the State of New York.

Eugene DeAngelis, MD, Bronxville. Died September 13, 1991; age 76. Dr DeAngelis was a 1939 graduate of Northwestern University Medical School, Chicago, Illinois. He was a member of the New York Academy of Medicine, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Grace Frank, MD, New York. Died July 22, 1991; age 79. Dr Frank was a 1938 graduate of the University of Western Ontario, Faculty of Medicine, London, Ontario, Canada. She was a Diplomate of the American Board of Psychiatry and Neurology. Her memberships included the American Psychiatric Association, the American Academy of Child and Adolescent Psychiatry, the Medical Society of the County of Queens, and the Medical Society of the State of New York. **Edith Millicent Forsyth, MD**, Brookhaven. Died September 24, 1991; age 58. Dr Forsyth was a 1956 graduate of the Medical School University of Birmingham, Birmingham, England. She was a Diplomate of the American Board of Family Practice and a Fellow of the American Academy of Family Physicians. She was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Arthur Winfield Glick, MD, New York. Died May 8, 1991; age 86. Dr Glick was a 1931 graduate of the State University of New York at Buffalo School of Medicine and Biomedical Science. He was a Diplomate of the American Board of Dermatology, Inc. His memberships included the New York State Dermatological Society, the American Academy of Dermatol-

ogy, the American Society of Legal and Industrial Medicine, the Society for Investigative Dermatology, the New York County Medical Society, and the Medical Society of the State of New York.

Neville A. Griffith, MD, Brooklyn. Died May 29, 1991; age 81. Dr Griffith was a 1940 graduate of McGill University, Faculty of Medicine, Montreal, Quebec, Canada. He was a Diplomate of the American Board of Dermatology, Inc. His memberships included the New York State Dermatological Society, the American Academy of Dermatology, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Henry James Herzog, MD, Lockport. Died May 19, 1991; age 81. Dr Herzog was a 1937 graduate of Friedrich-Wilhelms Universitaet Medizinische Fakultat, Berlin, Germany. He was a member of the New York Academy of Medicine, Medical Society of the County of Niagara, and the Medical Society of the State of New York.

George R. Lovell, MD, Pittsford. Died August 15, 1991; age 68. Dr Lovell was a 1950 graduate of New York University School of Medicine. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. His memberships included the New York Academy of Medicine, the New York State Society of Internal Medicine, the American Society of Internal Medicine, the Medical Society of the County of Monroe, and the Medical Society of the State of New York.

E. Terrill Montgomery, MD, Ponte Vedra Beach, Florida. Died February 10, 1991; age 86. Dr Montgomery was a 1930 graduate of the Virginia Commonwealth University, Medical College of Virginia, School of Medicine, Richmond, Virginia. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Jacob Ernest Nadler, MD, Kew Gardens. Died August 16, 1991; age 89. Dr Nadler was a 1930 graduate of the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Angiology, a Fellow of the American College of Cardiology, and a Fellow of the American College of Physicians. His memberships included the New York Academy of Medicine, the New York Cardiological Society, the Society for Experimental Biology and Medicine, the Pan American Medical Association, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

Edward Joseph Newman, MD, Poughkeepsie. Died August 26, 1991; age 59. Dr Newman was a 1957 graduate of Hahnemann University School of Medicine, Philadelphia, Pennsylvania. He was a Diplomate of the American

Board of Surgery and a Fellow of the American College of Surgeons. He was a member of the Dutchess County Medical Society and the Medical Society of the State of New York.

Harold David Paradis, MD, Pembroke Pines, Florida. Died January 6, 1991; age 76. Dr Paradis was a 1941 graduate of the University of Newcastle-Upon-Tyne Medical School, Newcastle-Upon-Tyne, England. He was a member of the American Society of Colon and Rectal Surgeons, the Suffolk County Medical Society, and the Medical Society of the State of New York.

William B. Talpey, MD, Rochester. Died July 19, 1991; age 65. Dr Talpey was a 1952 graduate of Washington

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Howard H. Volan, MD, Syracuse. Died March 23, 1991; age 88. Dr Volan was a 1926 graduate of the State University of New York Upstate Medical Center, Syracuse. He was a Diplomate of the American Board of Dermatology, Inc. His memberships included the New York Academy of Medicine, the Society for Investigative Dermatology, the American Academy of Dermatology, the Onondaga County Medical Society, and the Medical Society of the State of New York.

FROM THE LIBRARY

SYPHILIS OF THE GALL BLADDER AND BILE DUCTS

Syphilitic inflammation of the gall bladder and bile ducts is rare, except in the early secondary stage of syphilis when cholangitis is common. Of indubitably authentic cases there are of the congenital type 6, perhaps 9 (Rollston's analysis of Thomson's paper), and of tertiary cases thirteen, not including the present unique case, reported in the literature.

The inflammation may be *hereditary*; may attack the common duct *early* in the course of the *secondary* period of syphilis or this may happen *later* in the *secondary* period; or it may occur in the *tertiary* period.

The inflammation may be present at birth (hereditary syphilis) and is responsible for a certain proportion of the congenital anomalies (Thomson, Labadie-Lagrave) and malformations of the gall bladder and ducts either by having its initiation in the wall of the gall bladder and ducts or by starting in the neighboring structures in relation to them (glands, peritoneum, pancreas) and involving them secondarily. In the congenital cases the inflammation may take the form of an obstructive process outside the ducts and pressing upon them. The common bile duct is the part of the biliary system external to the liver most frequently so attacked. The cause of this form of obstructive process is syphilitic pancreatitis, enlarged glands in relation to the ducts or a productive inflammation of the peritoneum and tissues directly surrounding the ducts (Frerich's cases). Pressure may be exerted upon the hepatic duct by a gummatous process in the liver in the neighborhood of the duct. The inflammatory process may occur in the form of localized miliary gummata and round celled infiltration of the gall bladder and duct walls [Beck's cases, Biaz' two cases (probably) Roth's case (probably)], resulting in an obliterative inflammation of one or more of the ducts, usually the common duct. This last form may result from one of the two forms previously cited and is responsible for a few of the cases of congenital absence of the ducts though not for all, as defective development may occur with no luetic history obtainable. Thomson's view that syphilis is not an element of essential importance in the etiology of these cases of congenital absence of the ducts is probably correct.

RUSSEL S. FOWLER, MD
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CLASSIFICATION CODES

CC = Clinical Conference
CPC = Clinicopathologic Conference
CR = Case Report
ED = Editorial Commentary

EP = Essay in Pediatrics
ER = Essay Review
HIST = History of Medicine

LE = Letter to the Editor
LEN = Leads from *Epidemiology Notes*
NF = News Feature

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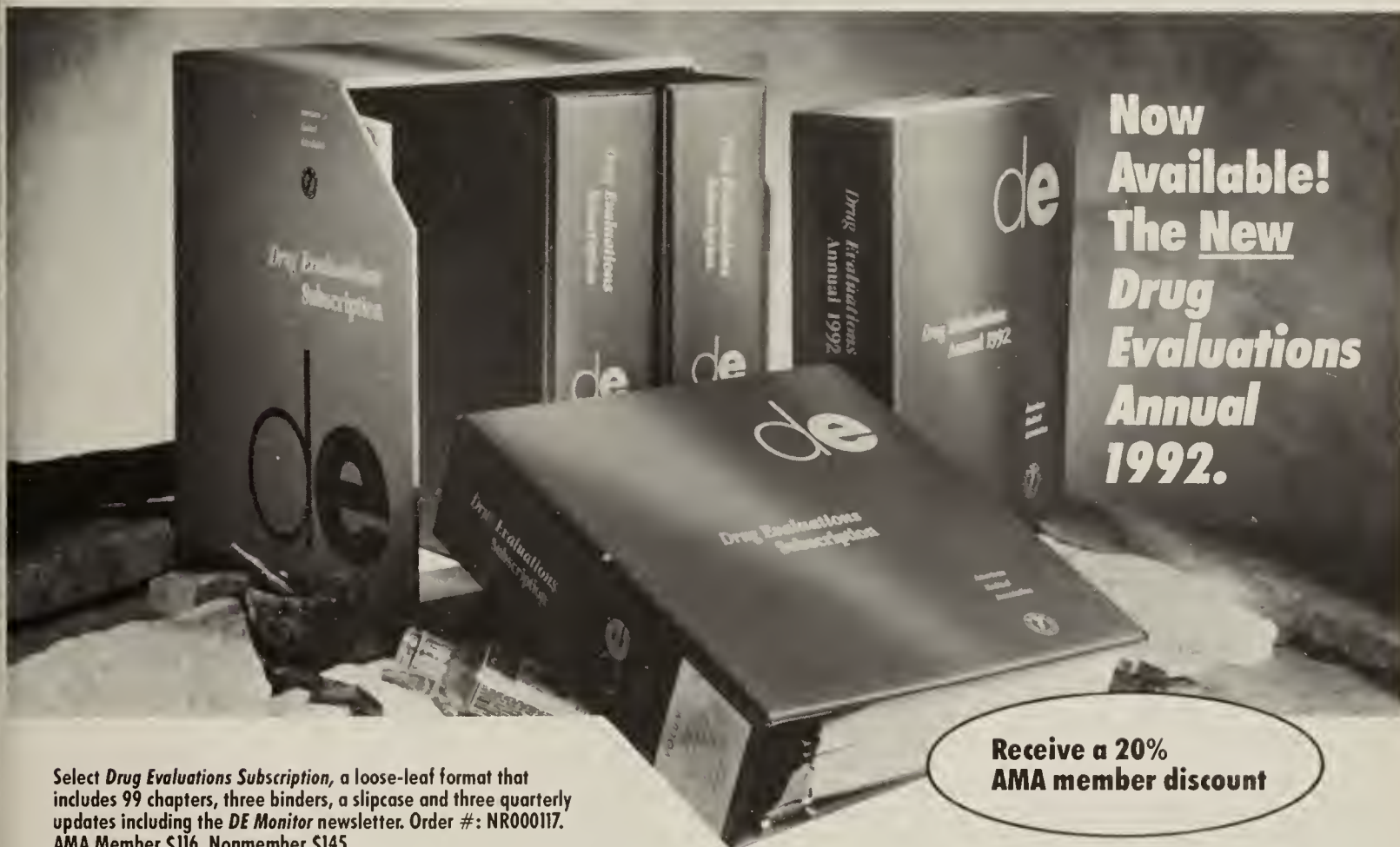
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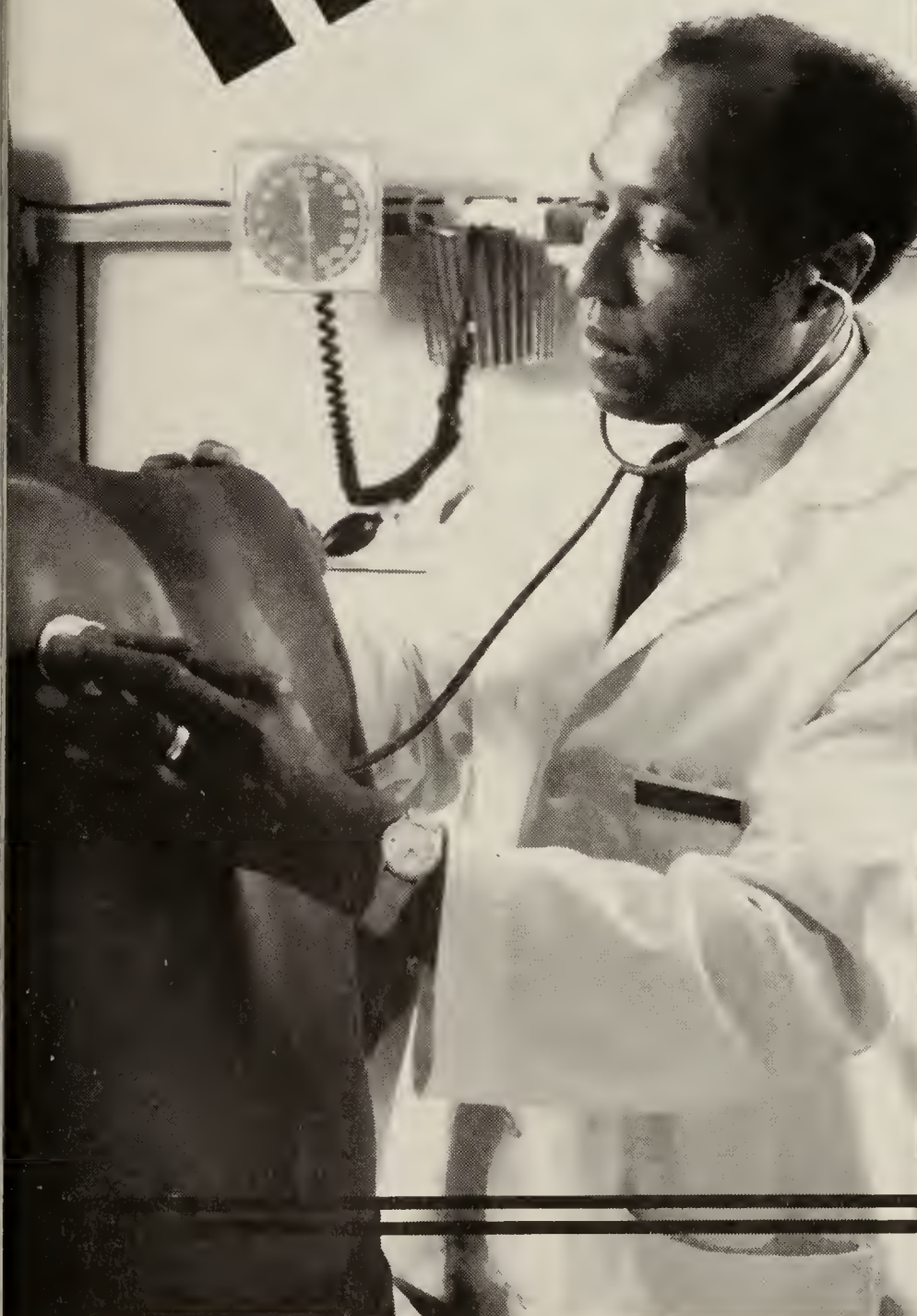
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INTRODUCTION

Triplicate prescription: Issues and answers

PETER B. FARNSWORTH, MD

Triplicate prescription programs now in effect in New York and in other states have come under fire by physicians and patient advocates, who assert that the programs not only have failed to meet their intended objectives—prevention of diversion and abuse of certain controlled drugs—but have become a hindrance to optimal patient care.

These critics of triplicate prescription regulations, which require physicians to file with state authorities copies of special prescriptions issued for scheduled drugs, also say that the regulations have had other unintended negative consequences. These consequences include violation of physician-patient confidentiality (because physicians must identify to state authorities those people for whom they prescribe scheduled drugs) and the creation of fear among physicians and patients alike. Many physicians have responded to an increasingly punitive regulatory environment by greatly reducing or even avoiding therapeutic use of controlled drugs, even though some of these agents, particularly the benzodiazepines, have greater efficacy and fewer side effects than alternative, uncontrolled drugs.

Many physicians say that they believe that their prescribing patterns, no matter how clinically defensible, will be subjected to nonmedical and possibly punitive review by state regulators if they elect to prescribe controlled drugs. They are concerned about this even though some of these drugs are considered to be the best available therapeutic choices for epilepsy, anxiety disorders, depression, and other medical conditions. In New York, for example, prescriptions for benzodiazepines, which were placed on the state's controlled list in 1989, have fallen sharply, whereas prescriptions for alternative drugs such as chloral hydrate, meprobamate, methypyrlon, and buspirone have risen greatly, although most

practitioners would agree that these medications are clearly inferior therapeutically to benzodiazepines. This trend in prescribing is troubling because it indicates a widespread reluctance among New York physicians to exercise legitimate medical judgment out of fear of regulatory action.

Patients have complained that triplicate prescription regulations jeopardize their privacy, stigmatize their medical problems, require them to see a personal physician every time they wish to renew a prescription, and force them to accept therapy with less-effective drugs because their physicians are reluctant to prescribe the more suitable, but controlled, medications. As a result, patients are paying for more office visits, losing more time from work because they must see their physicians more often, and enduring a lowered quality of life with the use of outmoded medications.

Worst of all, triplicate prescription programs have not blocked or even significantly reduced the availability of prescription drugs to street dealers and abusers, according to the latest research data. In fact, some of the data show that most illegal users of prescription medications do not depend on diversion of drugs from physicians. They obtain their supplies from street dealers, who in turn rely on alternative sources such as other states, illicit importation from other countries, or illegal laboratories.

The important issues raised by the increasing use of triplicate prescription as a regulatory tool were examined at a symposium convened by the Medical Society of the State of New York (MSSNY) in New York City in February of this year. The papers included in this supplement were developed out of presentations given at the symposium. (It should be noted that MSSNY invited the then New York State Commissioner of Health, David Axelrod, MD, and John Eadie, Director of the Division of Public Health Protection of the New

Address correspondence to Dr Farnsworth, Director, Division of Public Health and Education, Medical Society of the State of New York, 420 Lakeville Rd, Lake Success, NY 11042.

York State Department of Health, to address the symposium, but both men declined the invitations.)

Myrna M. Weissman, PhD, Professor of Epidemiology in Psychiatry at the College of Physicians and Surgeons of Columbia University, presents data from the Epidemiologic Catchment Area (ECA) study, in which more than 18,000 subjects in five cities were surveyed to determine the frequency of psychiatric disorders, including alcohol and drug abuse. Dr Weissman reports, for example, that although California has the nation's oldest (1939) triplicate prescription law, the state's largest city, Los Angeles, has a higher rate of prescription drug abuse than comparable communities in states that lack triplicate prescription programs. Moreover, nearly 100% of the subjects in the ECA study who admitted to abuse of or dependency on a prescription drug said that they did not obtain the drugs from a physician. Although Dr Weissman cautions that the ECA study was not designed to examine the impact of triplicate prescription legislation, she adds that in the case of California's triplicate prescription law, the ECA study provided data enabling investigators to analyze the law's effect on a large urban community.

Harold I. Schwartz, MD, Director of the Department of Psychiatry at Hartford Hospital and Associate Chairman of the Department of Psychiatry at the University of Connecticut School of Medicine, addresses the claim by proponents of New York's triplicate prescription regulation that its use has been responsible for reductions in drug diversion and inappropriate prescribing. He explains that New York's triplicate prescription regulation is not so much driving down diversion and inappropriate prescription as it is causing physicians to lower or halt their prescribing of controlled medications out of fear of state regulators. Dr Schwartz discusses the results of a study conducted at New York's Beth Israel Medical Center during the first three months of the benzodiazepine regulation. In all but one of the 24 cases clearly related to triplicate prescriptions, patients presented because their clinicians had refused to continue prescribing a benzodiazepine. Dr Schwartz also cites the results of a Gallup survey of 200 New York State physicians, in which only 9% of the physicians polled thought that their patients had benefited from the triplicate prescription regulation, whereas more than half thought their patients had suffered as a result of it. In effect, Dr Schwartz says, triplicate prescription in New York is having a chilling effect statewide on the legitimate and conscientious medical judgment of physicians.

Reina Berner, MSW, ACSW, appears here as an advocate for patients who have been adversely affected by triplicate prescription programs. Ms Berner, who is Executive Director of The Epilepsy Institute in New York, reports that she has received many letters from patients with epilepsy and other seizure disorders who are deeply concerned that the registration of their names with the state not only violates their privacy but serves to stigmatize them further as people with brain dysfunctions. For example, Ms Berner says, people with epilepsy often do not tell their employers that they have the disorder because they do not wish to allow such private and potentially damaging information to be

entered into computer records to which others have access. The Epilepsy Institute has followed the triplicate prescription issue, Ms Berner says, because of the use of some benzodiazepines as anticonvulsants. Since 1989, when benzodiazepines were added to New York's list of controlled medications, many people with seizure disorders that respond well to this class of drugs have complained of hardship in obtaining and/or filling prescriptions, Ms Berner says. As a result, she adds, patients have been forced to accept treatment with alternative drugs that may be less effective, more expensive, or have unacceptable side effects. Furthermore, Ms Berner says, patients have written to The Epilepsy Institute about losing jobs, having to go on public assistance, or undergoing costly hospitalizations for seizures that could have been controlled with a benzodiazepine.

Russell K. Portenoy, MD, Director of Analgesic Studies at the Pain Service of the Department of Neurology of Memorial Sloan-Kettering Cancer Center, argues that prescription drug regulations that do not allow for the special needs of cancer patients may worsen the already widespread problem of undertreatment of cancer pain. Although between 40% and 80% of cancer patients suffer from unrelieved pain, Dr Portenoy says that triplicate prescription and other state prescribing restrictions may deter physicians from sufficiently aggressive treatment of cancer pain. Dr Portenoy points out that it is often clinically necessary and appropriate for such aggressive analgesic therapy to include combinations of opioids, psychostimulants, and benzodiazepines, which are drugs whose use is regulated by triplicate prescription laws. Therefore, the prescribing patterns required to palliate cancer pain are the most liable to arouse the interest of state regulators, Dr Portenoy says.

Edgar H. Adams, ScD, until recently Director of the Division of Epidemiology and Prevention Research of the National Institute on Drug Abuse, points out that epidemiologic data suggest not only that fears about benzodiazepine abuse are excessive, but also that the impact of triplicate prescription programs on benzodiazepine abuse has been weak. Dr Adams is critical of proponents of triplicate prescription programs who carelessly interpret complicated federal government data about drug-related emergency treatment episodes to bolster the argument that triplicate prescription has significantly reduced the diversion of benzodiazepines to street abuse. For example, Dr Adams says, people who favor triplicate prescription fail to note epidemiologic data showing that a majority of benzodiazepine-related emergencies are suicide attempts, which differ in several ways from episodes related to drug dependency and withdrawal and do not reflect drug diversion. In fact, says Dr Adams, the data show that the rate of decline in benzodiazepine-related emergencies in New York, which was consistent with a national rate of decline begun in the 1970s, has slowed since the adoption of the benzodiazepine regulation; additionally, the proportion of New York patients seeking treatment for benzodiazepine withdrawal has increased.

Alan Breier, MD, Chief, Outpatient Program, Maryland Psychiatric Research Center, and Research Associate Professor of Psychiatry in the Department of Psychi-

atry at the University of Maryland School of Medicine, describes the neurobiologic basis of panic disorder, which is one of the anxiety disorders affecting 8.3% of adults each year, according to epidemiologic evidence. Although effective pharmacotherapy of panic disorder is available with the use of benzodiazepines, tricyclic antidepressants, or monoamine oxidase inhibitors, Dr Breier says that as many as four patients out of every five who have the disorder may not seek treatment because of the stigma attached to any type of mental illness. Dr Breier's discussion details the clinical components of panic disorder, outlines the factors to be considered in the selection of medication, and discusses the psychotherapies that have been most effective against panic disorder.

Rene F. Rodriguez, MD, President of the Interamerican College of Physicians and Surgeons, reports that Hispanic patients and their physicians have been disproportionately affected by the negative impact of New York's triplicate prescription program. Dr Rodriguez notes that the number of Hispanic physicians here is small compared with the number of patients they serve, and that the physicians have complained that triplicate prescription creates an additional inconvenience of extra paperwork in their already overcrowded schedules. He explains that the physicians are concerned not only about government scrutiny of their practices but also about patient confidentiality. Furthermore, Dr Rodriguez says that the physicians are worried that their patients, who are already medically disadvantaged by lower incomes, lack of insurance, and a higher-than-average incidence of reportable diseases, will suffer further hardship by being restricted in their access to acceptable and appropriate pharmacotherapy. A majority of New York's Hispanic physicians, according to Dr Rodriguez, believe that concern about drug abuse must not interfere with the appropriate medical use of psychoactive drugs. The result of the physicians' concerns, he says, is that a majority of the state's Hispanic clinicians now oppose triplicate prescription.

Theodore M. Collins, RPH, Associate Researcher at the Center for Health Systems Research and Analysis at the University of Wisconsin, illustrates how misguided is the notion that the adoption of a triplicate prescription program results in cuts in government expenditures for controlled drugs. Mr Collins argues convincingly that triplicate prescription programs have hidden costs and unintended effects; moreover, he points out, several less costly prescription monitoring programs already exist. These programs include the federal Drug Enforcement Administration's Automated Reports and Consolidated Order System, which keeps track of sales to pharmacies of all Schedule II and some Schedule III drugs; the federal Department of Health and Human Services' Medicaid Abusable Drug Adjudication System, which targets pharmacies, physicians, and patients who may be drug diverters; drug utilization review, by which Medicaid and other third-party payers of medical bills evaluate whether drugs are being prescribed appropriately and cost-effectively; and point-of-sale computer systems, which can enable pharmacists to link up with central computers at the institution paying for a prescription, to

examine patient data and to possibly identify "drug shoppers."

Mr Collins also comments that the use of alternative, unscheduled drugs can be more expensive than use of scheduled drugs both in cost per dose and in ineffectiveness or adverse effects leading to injuries and hospitalizations. Mr Collins concludes that triplicate prescription programs create more bureaucratic and administrative expenses than they remove, that they duplicate data gathering already available in several other monitoring programs, and that they are not as cost-effective and efficient as their proponents claim.

Sidney H. Schnoll, MD, PhD, Chairman of the Department of Substance Abuse Medicine and Professor of Medicine and Psychiatry at Virginia Commonwealth University and the Medical College of Virginia Hospitals, and his colleague Paula K. Horvatic, PhD, Director, Education and Training at the Division of Substance Abuse, propose that creative and innovative physician education programs to correct inappropriate prescribing patterns can be an effective alternative to state regulation. Instead of the usual continuing medical education program, which Drs Schnoll and Horvatic believe is too passive and even boring, they advocate a multifaceted approach using methods such as video, role-playing with actor "patients," computer-interactive case presentations, group problem-solving, and frequent changes in the learning setting. A model program being developed at the authors' institution, the Medical College of Virginia, is especially useful, the authors say, in that it teaches physicians how to prescribe for special, difficult patient populations such as recovering addicts, pain patients, the elderly, and pregnant women addicted to drugs.

At the symposium, Mitchell B. Balter, PhD, Clinical Professor in the Department of Psychiatry at Tufts University School of Medicine, expanded on the epidemiologic data about benzodiazepine use discussed by Dr Adams. (Dr Balter's presentation is to be published in its entirety in another journal in the near future; it is included in this volume in abstract form.) Dr Balter offered documentation showing that the prevalence and patterns of use of benzodiazepines in the United States have been and continue to be conservative and that these patterns fall well within international norms in spite of claims to the contrary by proponents of triplicate prescription programs. Moreover, Dr Balter said, the overall pattern of benzodiazepine use is guided by the nature of patients' illnesses rather than by drug abuse or dependence and that benzodiazepines may be significantly underused. Furthermore, Dr Balter asserted that strong concerns among physicians and patients about habitual use, dependency, and abuse of benzodiazepines are not supported by existing data because most people who take benzodiazepines are really ill and not recreational users seeking a psychotropic "high." Dr Balter also reported the results of a national cross-sectional study that found that 73% of persons with a high level of psychic distress caused by anxiety had received no treatment, which indicates that there are many people who could benefit from benzodiazepine therapy but are not receiving it.

Michael Weintraub, MD, Associate Professor in the Department of Community and Preventive Medicine and Pharmacology at the University of Rochester School of Medicine and Dentistry, spoke at the symposium; his presentation is included in this issue as an abstract because of a prior publication commitment. He used prescription data to argue that New York physicians are prescribing far less benzodiazepines now than they did a few years ago. He demonstrated that prescription of alternative agents such as meprobamate, methyprylon, chloral hydrate, buspirone, ethchlorvynol, butabarbital, and hydroxyzine has decreased or held steady in the United States as a whole but has increased substantially or greatly in New York. Use of alternative agents, according to Dr Weintraub, has gone up in New York in response to the state's triplicate prescription restrictions, even though these alternatives are generally accepted as less effective, less safe, and potentially more abusable than newer agents like the benzodiazepines.

Richard S. Blum, MD, a clinician specializing in internal medicine and clinical pharmacology, revealed that physicians all across New York State have told him that because of the triplicate prescription regulation, they are no longer prescribing their drugs of first choice.

Dr Blum says that these physicians, fearing potential state sanctions, are prescribing alternatives that are clearly inferior to the first-choice medications, are referring patients with anxiety disorders to psychiatrists, are sending patients to an emergency room to obtain a benzodiazepine prescription, or are refusing altogether to prescribe scheduled drugs because they feel that the criteria that could provoke an investigation are arbitrary. His presentation is included in this volume in an abstract because it will be published in another journal at a later date.

It is clear from the wealth of hard data presented at this symposium that triplicate prescription programs, in New York and elsewhere, are simply not practical for the prevention or control of prescription drug diversion and abuse, or for the counseling of physicians with inappropriate prescribing patterns. Other data gathering and physician-instruction systems are already in place or available; properly used, they can be effective against diversion and inappropriate prescribing without interfering with the legitimate and conscientious practice of medicine and, most importantly, without penalizing patients who need and can benefit from the latest and most efficacious forms of pharmacotherapy.

Triplicate prescription in New York: History and review

PETER B. FARNSWORTH, MD

Triplicate prescription in New York State has its origins in the period of antinarcotic fervor that affected this country during the early 1900s. From the turn of the century until just before the First World War, public fear of drug abuse had been growing rapidly, and the pressure was on for increased government regulation of narcotics. At first, lawmakers decided that restriction of narcotic transactions to licensed health practitioners was one solution to the drug problem.¹ Legislators generally believed that framing legal rules for the practice of medicine was impractical, and physicians were allowed to prescribe narcotics as they saw fit. However, as public fear of narcotics continued to rise, a small percentage of physicians was blamed for contributing to the drug problem by selling narcotics to patients. Although these physicians argued that they were exercising their medical judgment as licensed prescribers, a frightened electorate demanded quick action from politicians in New York and elsewhere to limit access to narcotics.^{1(pp93-94)}

EARLY LEGISLATION: 1914 TO 1919

In New York, one of the results of this ferment was the Boylan Act of 1914, which mandated, in part, that physicians be provided with state-issued order blanks to be used for the prescription of "chloral, opium or any of its salts, alkaloids or derivatives or any compound or preparation of any of them"² The prescription blanks were serially numbered in duplicate, with one copy given to the patient and the other copy kept on file by the physician for five years. The physician's file was open to inspection by state authorities at any time. It was also stipulated that no prescription for controlled narcotics could be issued until the physician had conducted a physical examination of the patient.^{1(p103)} Most people do not know that the final version of the Boylan Act was a revision of the first, introduced in 1913, which was vehemently opposed by physicians because it contained unprecedented legislative restrictions on prescribing rights. One restriction, for example, would have prohibited physicians from prescribing narcotics for longer than three weeks. Any continuation of such medication after that time would have had to be approved by a local health department.^{1(p113)}

The Boylan Act was superseded by the first Whitney law in 1917, which specifically stated that physicians could prescribe for the "comfort" of addicts,^{1(p114)} reflecting a contemporary view of addiction as a medical problem. However, the law also mandated the registration of addicts, requiring that physicians furnish a list of their addicted patients each month to the state.^{1(p114)} One legal authority noted that the explicit placement of addicts under the supervision of a physician resulted in a 50% reduction in the number of court cases for illegal possession and checked underworld exploitation of addicts' needs.^{1(p121)}

The trend toward medical control of the methods of addiction treatment was doomed, however, by the rapidly growing forces of Prohibition. The passage of the federal Harrison Narcotics Act in 1914 was hailed by many in the medical community because it mandated registration of all prescribers, dispensers, and manufacturers of narcotics. In spite of the act's bothersome record-keeping requirements, most physicians believed that adherence to the act would strengthen their control over potent medications.^{1(p121)} However, as the years passed and the Harrison Act's powers were gradually strengthened by amendments, physicians were dismayed to realize that federal agents were mainly interested in penalizing practitioners who prescribed large amounts of narcotics. For example, in 1915, less than a year after adoption of the Harrison Act, federal regulators promulgated rules by which pharmacists were warned to inspect prescriptions closely to determine whether the amount of the drug prescribed was "excessive."^{1(p122)} When one pharmacist complained that the regulation was too general and vague, the US Treasury Department reacted by creating a new regulation that physicians should state on prescription forms their reasons for prescribing an "unusual quantity" of a drug; moreover, the regulation called for the physician to show "good faith" by "a decreasing dosage or reduction of the quantity prescribed from time to time."^{1(p122)} By early 1919, increasing federal control and a strict ruling by the Supreme Court essentially outlawed maintenance of addiction everywhere. Even reduction and outpatient treatment were forbidden.^{1(p120)}

TRIPPLICATE PRESCRIPTION IN NEW YORK: 1959 TO 1986

Triplicate prescription was first recommended in New York in 1959 by the Joint Legislative Committee on

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Narcotics Study. It was intensively debated until 1972 when it became law as part of the state's Controlled Substances Act. At that time, triplicate prescription was challenged as an infringement on physician/patient confidentiality; its enforcement was held up until 1977, when the US Supreme Court ruled in favor of the state department of health, allowing triplicate to commence in New York.³

Physicians in New York initially opposed the imposition of triplicate prescription as an interference by the state in the practice of medicine. Gradually, however, triplicate became accepted for two reasons: It involved a relatively small percentage of overall prescriptions, and it was truly a peer-review process and considered to be fair. In the early years of triplicate, the New York State Department of Health (NYSDOH) furnished quarterly printouts to county medical societies, enabling them to track the prescribing patterns of their members and to take corrective action against those members whose prescribing was excessive or inconsistent with their type of practice. The use of the state-furnished printouts gave the peer-review process an effective educational tool to help certain physicians change outmoded or careless prescribing habits. More importantly, this reviewing system enabled qualified medical practitioners to evaluate, educate, and correct their colleagues. Those physicians who did not comply with the peer-review process were referred to the appropriate authorities. By the mid-1980s, however, the state had gradually stopped supplying the quarterly printout forms to the local medical societies, and the peer-review process broke down.

THE CURRENT PROGRAM

In 1987, New York State Commissioner of Health Dr David Axelrod, who apparently equated a high volume of benzodiazepine prescriptions with abuse, decided to promulgate a new regulation adding benzodiazepines to the list of controlled substances to be covered by triplicate prescription. The New York State medical community, knowing benzodiazepines to be useful and safe Schedule IV medications for the treatment of a variety of medical conditions, opposed this new regulation. Moreover, many New York physicians came to believe that the NYSDOH had placed an enormously popular drug class on triplicate prescription to get more physicians to buy triplicate books, which would quickly increase the agency's revenues. (The NYSDOH has denied this allegation.)

Before the 1988 deadline for the placing of benzodiazepines on triplicate, representatives of the Medical Society of the State of New York (MSSNY) met with Dr Axelrod to present him with an alternative to the upcoming benzodiazepine regulation: a substantial, state-wide program to educate all MSSNY members in the proper use of benzodiazepines. Unfortunately, Dr Axelrod did not accept this alternative and proceeded with plans to impose his new benzodiazepine triplicate prescription regulation.

In spite of the NYSDOH's lack of interest, MSSNY proceeded with its own continuing medical education

(CME) program for benzodiazepines, which included the following components:

- A three-hour Category I CME program on the proper use of benzodiazepines, mailed to 40,000 physicians in New York State. This package included an authoritative booklet on benzodiazepines and a test for physicians to complete and return to MSSNY for three hours of CME credits.
- An all-day symposium on benzodiazepines to which physicians in education were invited.
- A slide/text educational packet incorporating the symposium proceedings, produced and distributed to symposium attendees and others for ongoing education in the appropriate use of benzodiazepines.
- An audiocassette containing information on the proper use of benzodiazepines, produced and mailed to all practicing physicians in New York State.

With these efforts having failed to satisfy Dr Axelrod, MSSNY decided to bring suit against the NYSDOH. In its lawsuit, MSSNY argued that Dr. Axelrod had exceeded his regulatory authority under the Controlled Substances Act of 1972.⁴ Unfortunately, the courts once again ruled in favor of the state, and benzodiazepines went on triplicate prescription in 1989.

TRIPPLICATE REGULATION SINCE 1989

MSSNY continues to challenge New York State's triplicate prescription program, which we believe is simply not effective in controlling or reducing diversion of prescription drugs into the illegal market. We also believe that the NYSDOH has irresponsibly created a climate of fear of regulation among physicians. The NYSDOH claims that benzodiazepine prescriptions have fallen steeply since 1989, indicating a lessened supply to street dealers and drug abusers. We question whether that reduction has occurred because of reluctance by physicians to prescribe controlled drugs out of fear of state investigation, resulting in a denial of these medications to patients with legitimate medical needs for them. We also question the cost-effectiveness of the triplicate program and can demonstrate that a majority of surveyed physicians are opposed to it.

PHYSICIANS' UNEASE

Part of the uncertainty about regulation felt by physicians comes from the statements of the regulators themselves. For example, John Eadie, who is director of the Division of Public Health of the NYSDOH, stated his own criteria for investigation in 1990. In his words, the NYSDOH, through examination of triplicate prescription data, seeks to identify prescribing practices "... which appear to be very unusual, to be extremely excessive, or to have the implication of being illegal in nature."⁵ Mr Eadie's language is very broad and general and offers little guidance to physicians.

Two recent cases illustrate that physicians' fear of overzealous regulation based on triplicate prescription data is not unfounded. In California in 1981, a family physician was charged by state regulators with overpre-

scribing controlled medications for his patients suffering chronic pain. The physician argued that regulators were applying enforcement standards that were too general and vague; furthermore, the physician argued that his medical intention was to relieve his patients of disabling pain, thus improving their quality of life and productivity in society. The state still found the physician guilty of overprescribing, although he had practiced medicine for over 20 years without any allegations of wrongdoing. By the end of the investigative process, which resulted in the physician's conviction on minor charges of overprescribing (the major charges were dropped by the state) the physician had spent well over \$100,000 in legal fees to defend his medical judgment.⁶

In New York in 1988, a prominent oncologist at a large teaching hospital was arrested in his office by two officials from the NYSDOH and charged with overprescribing controlled pain medications (Personal communication, RK Portenoy, May 1991). As the oncologist was being led out of his office, he showed the arresting investigators two of his cancer patients, each in severe pain, who had been waiting to see him. One was vomiting in a sink from intracranial cancer and the other was in tears from the pain of diffuse bony metastases. The oncologist was charged by the state with failing to fill out the triplicate prescription forms properly for 250 patients, all of whom had cancer, and of failing to notify the state of the names of patients who had been on narcotics for prolonged periods of time. If convicted, the oncologist faced up to \$2.5 million in fines plus censure or loss of his license to practice medicine. However, after 18 months of investigation, the state determined that the oncologist had made only clerical errors; otherwise, his practice was impeccable. The state quietly dropped the case, which cost the oncologist \$9,000 in legal fees.⁷

Another area of uncertainty about the regulation is the question of whether a physician may issue a prescription for a triplicate-related drug without seeing the patient each time. Subdivision (c) of Section 80.63 of part 80 of Title 10 (Health) of the Official Compilation of Codes, Rules and Regulation of the State of New York formerly stated that "No controlled substance shall be prepared prior to examination of the patient by the practitioner." In January 1991, that section was amended to read: "(1) No controlled substance prescription shall be *issued* [prepared] prior to the examination of the patient by the practitioner *except as otherwise permitted by this subdivision*. (2) *Once the initial examination has been completed, the frequency and necessity for future examinations prior to prescribing, either for the same acute or chronic condition, will be made by the practitioner utilizing generally accepted medical standards, including taking into account the drug to be prescribed and the patient's condition, history and disposition toward the use of controlled substances.*" Additional subdivisions to this rule describe other situations in which controlled substances may be prescribed.

In the event that a clinician decides that an examination is not necessary, the patient must still show up at the physician's office to pick up a new prescription unless some other means of transmitting the prescription form

has been arranged between the patient and the physician. For the clinician to mail the forms means a monthly procedure that is time consuming, impractical, and not secure.

What the regulation now does is to leave the decision about whether an additional examination is required up to the clinician, but the clinician does not know the standard to which he or she is held. This creates a great deal of anxiety in clinicians. Therefore, they very often take the conservative position of requiring patients to come in for an examination each time a new prescription is needed. This, in turn, imposes a terrible burden of time and cost on the patients.

The Commissioner of Health's claim that these frequent, repeat visits for prescription purposes only are not mandated by law is an empty assurance to practitioners who see more and more areas of their practices open to challenge by non-medically trained bureaucrats legally empowered to question any doctor's medical judgment.

COST-EFFECTIVENESS

The issue of cost-effectiveness has not been adequately documented by proponents of New York's triplicate program. The 1991-1992 New York State operations budget, for example, contains a \$2,770,900 item for the Bureau of Controlled Substances, which is primarily dedicated, under the NYSDOH, to the operation of the triplicate prescription program. The bureau's 1990 annual report shows that only four physicians were "completed" for prosecution. The report does not indicate whether these physicians were identified from triplicate prescription data. In the bureau's report for 1988 (before the placement of benzodiazepines on triplicate), again only four physician cases were "completed" for prosecution. The 1988 report also fails to say whether data gathered through the triplicate program were responsible for the action. New York State is in a severe budget crisis; even assuming that triplicate data were used to prosecute the eight physicians mentioned in the two years' annual reports, the ratio of budgetary costs to physician prosecutions is severely unbalanced. We also wonder just how many of the eight cases mentioned resulted in conviction.

PHYSICIANS UNSUPPORTIVE

A good test of the effectiveness of a triplicate prescription program is its acceptance among physicians because a majority of physicians must participate in the program to make it work. A recent survey showed that a majority of physicians who responded do not support New York's triplicate prescription program. In 1991, MSSNY polled approximately 9,000 people in the state on the issue of triplicate prescription. Eighty-six percent of the respondents were physicians practicing general, family, or internal medicine or psychiatry. Ninety-eight percent of those physicians possess and use triplicate prescription pads. By a ratio of four to one, the physicians surveyed found disadvantages in the triplicate program. Seventy-five percent said that triplicate prescription allows government to dictate the practice of medicine; 74% said the program consumes too much of

the physician's time for record-keeping; 64% felt that the program violates physician-patient confidentiality; 58% said that triplicate has had a detrimental effect on their practices; 56% complained that the program creates unnecessary monitoring of physicians; and 49% estimated that the program increases medical costs to patients. More than half of the physicians (53%) believe that their patients have been harmed by the placing of benzodiazepines on triplicate; only 17% mentioned a beneficial effect of the regulation. Interestingly, 72% of all respondents (including not only physicians, but also legislators, legislative aides, law enforcement representatives, and patient advocates) believe that the reporting requirements of the triplicate program have resulted in violations of physician-patient confidentiality. Eighty-three percent of all respondents stated that New York's triplicate program should either be revised or rescinded; 67% thought the program should be rescinded forthwith. Finally, only 15% of those respondents who found advantages to the triplicate program mentioned cost-effectiveness as a benefit to the state.

CONCLUSION

The facts show that New York's triplicate prescription program has major flaws. Its enforcement criteria are

imprecise and overbroad and have led, in at least one documented case, to an overzealous, protracted, and expensive prosecution of a respected physician found guilty of nothing more than clerical errors. Its cost-effectiveness has not been demonstrated, and those figures that we can obtain place the program's budgetary worth very much in doubt. Finally, a majority of New York physicians—and others—oppose triplicate prescription for a number of reasons already mentioned.

At a time when triplicate prescription already exists in nine states and is being considered in several other states and at the federal level, physicians owe it to themselves—and to their patients—to firmly challenge triplicate prescription laws as a significant danger to the conscientious and independent practice of medicine.

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Negative clinical consequences of triplicate prescription regulation of benzodiazepines

HAROLD I. SCHWARTZ, MD

The extension of the New York State triplicate prescription program to benzodiazepines in 1989 was surrounded by controversy. There was hope within the medical community that enactment of the regulation would be prevented by a lawsuit. That hope proved futile, and the regulation went into effect on January 1 of that year. It became clear that empirical evidence would be needed to assess the impact that this regulation was going to have on patient care.

We performed a study at Beth Israel Medical Center in Manhattan, reported previously,¹ in which we evaluated the psychiatric consultation notes of all emergency room evaluations for a three-month period, beginning two weeks after the triplicate regulation went into effect. We looked at all cases in which benzodiazepine use was felt to be part of the presenting problem. We also included in our sample walk-ins to the psychiatric clinic during the day and scheduled new evaluations in the psychiatric clinic. On the basis of those chart reviews and, when necessary, interviews with the clinician who had engaged in the emergency room interaction with the patient, we divided our cases into three categories: those that we felt were directly related to the benzodiazepine triplicate regulation, those that were probably related, and those that were not related.

Our sample included 59 cases, of which 24 were clearly related to the triplicate regulation. In all but one of those 24 clearly related cases, the patient presented because of symptoms or concerns that directly stemmed from the refusal by a clinician to continue prescribing a benzodiazepine in a previously established pattern. Of the 24 patients in our clearly related group, 18 were not substance abusers. Of those, six patients appeared to be suffering from the reemergence of an underlying anxiety disorder (anxiety disorder, adjustment disorder with anxious mood, or panic disorder by DSM-III-R criteria). Another three appeared to be experiencing the reemergence of an underlying anxiety disorder and/or protracted withdrawal. Three patients appeared to be dependent and in withdrawal (the dependency may have been iatrogenic). Another three were possibly dependent and were seeking a prescription in anticipation of withdrawal symptoms. One was possibly dependent and specifically seeking detoxification on a medical detoxifi-

cation service rather than a psychiatric one. One patient was in a frank organic psychosis apparently secondary to abrupt cessation of a benzodiazepine. Finally, one patient presented refusing to continue treatment with a benzodiazepine, which the clinician believed was necessary, secondary to concerns about confidentiality. Within the 24 clearly related cases, six persons were determined to be substance abusers. Of these, two appeared to be in acute withdrawal, three appeared to be in protracted withdrawal, and one appeared to be a nondependent, mixed-substance abuser seeking a new source of medication.

The numbers presented above do not adequately convey the human cost of the triplicate prescription regulation. The following case reports may be useful in that regard.

CASE REPORTS

Case 1. A 52-year-old married man had a long history of panic attacks, agoraphobia, and obsessive-compulsive disorder. He had been referred to a group for his panic disorder after his symptoms worsened after the death of his mother and his second myocardial infarction six-years before our study. He had been medicated with alprazolam 0.5 mg, three times a day. On this regimen, he was less anxious and suffered no panic attacks; however, he often had exacerbations of severe anticipatory anxiety, such as when his wife and various siblings had been hospitalized. For the past several years, he had had his medication monitored at a neighboring municipal hospital, where he also received his alprazolam at no cost. In January of 1989, after the regulation went into effect, he reported that his alprazolam dosage had been decreased to 0.5 mg twice a day, although his anxiety at that time was high. He reported that his psychiatrist told him that "she is not allowed to write for as much alprazolam because of changes by the State of New York." His alprazolam was not readjusted in spite of his protest and his increased level of anxiety, leading him to seek additional assistance in our emergency room.

Case 2. A 56-year-old Hispanic woman presented to our walk-in clinic complaining of feelings of nervousness, irritability, difficulty sleeping, muscle twitching, and muscle tension. Four weeks before presentation, her physician had abruptly discontinued prescribing lorazepam 4 mg per day (total) which he had been

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prescribing for her for several years. Her condition had deteriorated from that time to the point where she now felt too anxious to shop, cook, clean, or carry on with the activities of daily living. She had first been placed on benzodiazepines ten years earlier when she felt jumpy and nervous constantly after the onset of her menopause. On examination she was observed to be tense, anxious, irritable, strident, and preoccupied with obtaining lorazepam. The impression on evaluation was that the patient had a generalized anxiety disorder which had been successfully managed with lorazepam and that she was now suffering from her previously treated anxiety and secondarily from lorazepam withdrawal.

Case 3. A 62-year-old widowed Hispanic female had a history of three psychiatric hospitalizations. She was diagnosed as suffering from recurrent depression with psychotic features and dysthymic disorder. She had multiple medical problems including coronary artery disease (which had required quadruple bypass surgery some years before), severe asthma, osteoarthritis, hiatal hernia, peptic ulcer disease, and hypertension. She had functioned remarkably well for several years on low doses of lorazepam and, when necessary, tricyclic antidepressants, in spite of multiple severe stresses. These stresses included the prolonged decline and death of her husband after several crippling cerebrovascular accidents, the death of her father and cousin, and the murder of her brother. After implementation of the triplicate prescription regulation, the patient refused to continue taking lorazepam in spite of increased anxiety around the anniversaries of the deaths of her husband, father, and brother. She feared that registration of her name in Albany as a "drug user" would in some way disgrace her and her family, particularly if this information were released in the event of her death. All attempts to correct the patient's misperceptions failed, and she refused to fill a triplicate prescription for lorazepam in spite of her physician's emphatic advice to do so. Out of concern for the possibility of withdrawal in this elderly and frail patient, her physician started her on phenobarbital with the intent to taper slowly.

DISCUSSION

Increased regulation of benzodiazepine prescribing carries risks, as our findings and these case reports demonstrate. Cases 1 and 2 illustrate the adverse effect on proper prescribing of benzodiazepines that can result from intimidation of physicians by the triplicate regulation. In case 1, a patient whose panic disorder had been controlled by alprazolam, administered at a recommended dosage, had his dosage reduced to a lower-than-recommended and clinically inadequate level by a physician who acknowledged that she felt pressured by the regulation to reduce her prescribing of the drug. In the second case, a patient with a generalized anxiety disorder controlled by lorazepam had her medication abruptly discontinued in spite of clear admonitions against abrupt discontinuation in the package insert, resulting in severe deterioration of her condition. Another risk, that of having patients refuse to take needed medication because of fear of being stigmatized, is exemplified by case 3, in which a patient with recurrent depression had

been able to function on low doses of lorazepam in spite of her condition and multiple severe stresses, but refused to continue to take the drug on learning that the triplicate program required that her name be registered in a government-run computer system.

Additional supporting evidence has also emerged. Prescription data from Medicaid, IMS Ltd., and Blue Cross/Blue Shield indicate that the prescribing of benzodiazepines in New York has declined by 44% since implementation of the regulation.² Supporters of triplicate regulation consistently assert that decreases in the use of any controlled substance reflect decreases in inappropriate or illicit use and as such represent a "victory" in the war on drugs.³⁻⁵ However, no empirical evidence exists to support this conclusion. To the contrary, a growing body of data, some of which we report below, argues that this substantial decline in benzodiazepine prescribing reflects an unfortunate impact on the legitimate and appropriate prescribing of this class of medication. The decline in benzodiazepine prescribing has been accompanied in New York by an increase in the prescribing of buspirone, meprobamate, hydroxyzine, chloral hydrate, hypnotic barbiturates, methypylon, and ethchlorvynol.^{2,6} There is suggestive evidence that sales of distilled spirits increased during the first four months after the regulation went into effect, pointing to a self-medication phenomenon.⁶ These types of findings coincide with evidence that adverse publicity about the use of benzodiazepines in Finland and restrictions on benzodiazepine prescribing there during the 1970s was accompanied by a rise in alcohol consumption in that country.⁷ Farid and Bulto have reported that in Britain, media attention and the possibility of legal action have led practitioners to reduce or stop the prescribing of benzodiazepines precipitously, leading in turn to severe worsening of anxiety disorders among patients and increased hospitalizations for withdrawal.⁸

One can speculate why physicians engaged in appropriate prescribing of benzodiazepines would abruptly change their practices in response to a triplicate prescription regulation. Concerns about confidentiality and the cumbersomeness of the new prescription procedures may be partial explanations. It is possible that, in an era of increasingly punitive regulation of medical practice, physicians can be dissuaded from what they believe to be good medical practice out of fear of regulatory agencies. As one supporter of triplicate prescription programs has written, the dramatic reduction in overall prescribing is perhaps most attributable to the "chilling effect" of the knowledge that a copy of the prescription goes to the state.⁵ That chilling effect was obviously experienced by, at least, our one patient who refused to fill an appropriate triplicate prescription out of fear of the disgrace of being registered with the state as a drug user.

It is possible to go beyond speculation in assessing the impact of this regulation on physician attitudes and behaviors and on patients. The following set of data consists of the results of a Gallup survey of 200 primary care physicians and psychiatrists in New York State conducted in January 1991.⁹ The objective of this survey was to ascertain current physician reactions to the triplicate prescription regulation after two years of

experience with it and to ascertain physician perceptions of the effect of the regulation on patients (Table I).

Fully 93% of the respondents were either very familiar or at least fairly familiar with the regulation. When asked whether the triplicate prescription regulation had led to a change in prescribing behavior, nearly half of the respondents reported that their prescribing of benzodiazepines had decreased. Another half reported no change. It is worth noting that psychiatrists appear to be less affected; only 27% of the respondent psychiatrists reported a decrease in their prescribing, in contrast to 57% of general practitioners. This result may reflect the somewhat greater comfort or familiarity of psychiatrists with this class of medication.

The respondents reported that a variety of medications are being substituted for benzodiazepines (see Table II), including buspirone, fluoxetine, meprobamate, and nonsteroidal anti-inflammatory drugs. In the "other" category, respondents mentioned ethchlorvynol, antihistamines, antidepressants, and phenobarbital as substitutes that are being prescribed. Asked, without prompting, to report advantages of the regulation, 17% reported that it reduces inappropriate prescribing of benzodiazepines, and 9% said it targets drug-abusing patients. Fully 64% of the respondents reported

TABLE II. Alternative Medications Prescribed

	Total (%) (n = 83)
Nonsteroidal anti-inflammatory drugs	8
Buspirone (BuSpar®)	46
Fluoxetine (Prozac®)	12
Meprobamate	18
OTC products	6
Other	60
No other drug therapy	10
Total	160*

*Total exceeds 100% because of multiple responses.
Source: The Gallup Organization, Inc., 1991.

no advantage to the regulation. It is of interest that 4% referred to the large savings which New York State has realized by virtue of decreased prescriptions charged to Medicaid or other state-funded programs.

When asked about disadvantages of the New York State triplicate prescription legislation, 57% of the respondents reported that it increased costs to patients, 63% were concerned about patient confidentiality, and 86% were concerned about the amount of time that it takes to fill out triplicate prescriptions. Of the respon-

TABLE I. Gallup Survey Questions

How familiar are you with the New York Triplicate Prescription legislation enacted January 1, 1989? Would you say you are. . . (read)

1. Very familiar?
2. Fairly familiar?
3. Not too familiar?
4. Or not at all familiar? (terminate interview)

Has your prescribing use of benzodiazepines increased, decreased, or stayed the same since the triplicate prescription regulation went into effect?

If decreased, ask:

If your use of benzodiazepines has decreased, what alternatives have you prescribed instead? (do not read answers)

What advantages, if any, do you feel the triplicate prescription regulation provides? (do not read answers)

What disadvantages, if any, do you feel the triplicate prescription regulation creates? (respondents were read the following:)

	Yes	No
a. Increasing the cost burden to patients	1	2
b. Violating patient/physician confidentiality	1	2
c. Consuming too much of the physician's time	1	2
d. Patient benzodiazepine withdrawal concerns	1	2
e. Unnecessary physician monitoring	1	2
f. Legislators inappropriately dictating the practice of medicine	1	2

Up until now, the questions have been related to the physicians' perspective of the regulation. Now, we are asking the physicians' opinion with regard to patients.

Do you feel this regulation has benefited patients, caused them to suffer, or had no effect?

If suffered, ask:

How have your patients suffered as a result of the triplicate prescription regulation? (do not read)

I would like to read you some disadvantages to patients others have suggested. For each, please tell me whether you feel it is a disadvantage for the patients you treat. (respondents were read the following:)

	Yes	No	Not Sure
a. Increased costs such as office calls, transportation costs, etc.	1	2	3
b. Denied access to appropriate medication	1	2	3
c. Violation of patient confidentiality	1	2	3
d. Consumes more of patient's time	1	2	3
e. Unnecessary physicians monitoring	1	2	3
f. Other more expensive medications must be prescribed	1	2	3
g. Other less safe medications must be prescribed	1	2	3
h. State is inappropriately dictating the practice of medicine	1	2	3

Since all benzodiazepine prescriptions are recorded in Albany and state and federal officials can easily identify them, do you feel this is a violation of physician-patient confidentiality?

Do you support the adoption of a triplicate prescription regulation at the national level?

What changes, if any, should there be in the New York State law? (do not read)

dents, 78% were concerned about inappropriate regulation of the practice of medicine. Probably of greatest importance is the finding that 41% of the respondents expressed concern that patients may experience withdrawal as a result of the regulation's limitation of their continued access to benzodiazepines.

When asked what effect the regulation has had on patients, only 9% of the respondents thought that their patients had benefited from it, whereas a majority (55%) were concerned that patients had suffered. When asked to specify how patients suffer (see Table III), the respondents emphasized that the triplicate prescription regulation increases cost to the patient, has led to violations of patient confidentiality and to unnecessary monitoring, and consumes unwarranted amounts of the patient's time. Again, the most important finding here is that 36% of the respondents believed that their patients had been denied access to appropriate medication and that other more expensive and less safe medications are being prescribed as substitutes. In the same survey, when the list of responses in Table III was used as a prompt to the respondents, the rates of responses to these items increased dramatically, and 56% of the physicians and psychiatrists agreed that their patients had been denied access to appropriate medications. Of the respondents, 31% were concerned that other, more expensive medications must be prescribed; 42% reported that less safe medications must be prescribed.

Of the respondents, 80% expressed a belief that recording of prescriptions is a violation of physician-patient confidentiality, and 85% reported opposition to triplicate prescription legislation on a national level. The vast majority of respondents were in agreement that New York State's triplicate prescription regulation ought to be changed by rewriting the law, rescinding the regulation, or through other means.

In summary, virtually all supporters of multiple copy prescription programs cite reductions in overall prescribing of Schedule II substances as a victory in combating drug abuse, without distinguishing between reductions in appropriate, as opposed to abusive, prescribing practices. Given that victories in the war on drugs are so hard to come by, it may be that regulators are seduced by any numbers that appear to move in the right direction. The

TABLE III. How Patients Have Suffered

Areas of Concern	Total (%) (n = 111)
Increased cost such as office calls, transportation costs, etc.	40
Denied access to appropriate medication	36
Violation of patient confidentiality	21
Consumes more of patient's time	24
Unnecessary physician monitoring	14
Other, more expensive medications must be prescribed	7
Other, less safe medications must be prescribed	7
State is inappropriately dictating the practice of medicine	17
Other	45
Total	211*

*Total exceeds 100% because of multiple responses.
Source: The Gallup Organization, Inc., 1991.

extension of such programs to benzodiazepines may mark an additional spurious victory, but the victory comes at significant cost: The costs (both financial and psychic) of these programs to patients can be high. In attempting to redress what are essentially criminal justice problems through the regulation of legitimate clinical practice, regulatory agencies can and do ultimately deprive deserving patients of appropriate, legitimate, and efficacious treatments.

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The effect of drug regulation on the management of cancer pain

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As a model of clinical activity, the management of cancer pain represents an exceptional opportunity to evaluate the influence of regulatory policies on professional practice and patient outcome. Cancer pain is a prevalent and compelling symptom, and the clinical imperative to provide relief is widely accepted, particularly in the setting of advanced disease. Although medical experts and regulators generally concur that controlled prescription drugs are both essential in this population and highly effective when administered optimally, numerous surveys have demonstrated that pain is inadequately relieved in a large proportion of cases. A detailed analysis clarifying the degree to which these documented inadequacies in management relate to the regulation of controlled drugs may have important implications for both policymakers and clinicians.

This analysis, however, must place the role of regulation in context. It is evident that the failure of a patient to obtain adequate relief from cancer pain is potentially related to a large number of interacting factors, only one of which may be the influence of regulatory policies on the prescribing practices of the treating physician. To understand the role of regulation, it is necessary to clarify the influence of these other factors. Efforts are needed to address a range of problems that contribute to the persistence of unrelieved pain among patients with cancer.

EPIDEMIOLOGY OF CANCER PAIN

Numerous surveys have established that pain is experienced by 30%–50% of cancer patients with relatively early disease and 70%–90% of patients with far advanced disease.^{1,2} Although pain is the most dreaded of symptoms in this population, surveys indicate that relief is possible for most of these patients. Of patients treated by specialists in cancer pain management, 70%–90% obtain adequate relief, most through the proper use of opioid drugs.^{3–7} An enormous body of clinical experience has established that long-term opioid therapy for cancer pain is seldom compromised by the development of tolerance or intolerable side effects and is virtually never accompanied by drug abuse or addiction. On the basis of this experience, the use of opioid therapy in this population has been strongly endorsed by experts in cancer pain and numerous professional organizations.^{8–11}

The conclusion that opioid therapy is both accepted in principle and highly efficacious in practice stands in stark contrast to the evidence that cancer pain is inadequately relieved in a large proportion of patients.^{1–3,12–17} For example, a survey of 1,103 consecutive admissions to a hospital dedicated to the care of patients with advanced cancer determined that 73% had pain and 38% had severe pain.¹² Similarly, a survey of 100 patients admitted to a hospice in the United Kingdom found that unrelieved pain usually described as severe or excruciating was experienced by 90% for more than four weeks and by 77% for more than eight weeks.¹³

CAUSES OF UNRELIEVED CANCER PAIN

Numerous factors have been identified that may substantially reduce the likelihood of a favorable response to analgesic therapy in the cancer population.¹⁸ In some patients, pain remains unrelieved because of the refractory nature of the pain syndrome itself. Although patients with truly refractory pain represent no more than 20% of those referred to specialized units (and probably far less in an unselected population), this group must be recognized in an analysis of factors contributing to unrelieved pain.

Apart from the small group with truly refractory pain, most patients with unrelieved cancer pain could obtain adequate relief if available therapies were applied optimally. It may be possible therefore to identify potentially reversible factors that impede the realization of this objective. Clinical observation suggests that these factors can be divided into those related primarily to patient behavior and those related primarily to clinician behavior¹⁹ (see Table I).

Patient-related Factors Contributing to Unrelieved Cancer Pain. Recognition of patient-related factors that contribute to persistent cancer pain is necessary both to develop educational programs and to provide a context for a discussion of those influences, such as regulatory policies, that predominantly affect clinician behavior. Patient noncompliance is common in all of therapeutics, and some of the causes of noncompliance with analgesic treatment regimens presumably parallel those causes observed in other settings, including the complexity of the therapy and the occurrence of uncomfortable side effects.

Other influences, however, may be unique to the experience of cancer pain or to the use of opioids to treat it. For example, experienced clinicians often note

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TABLE I. Factors Contributing to the Prevalence of Unrelieved Cancer Pain

Patient-related Factors

Ineffectual pain reporting

1. Caused by stoicism
2. Caused by the desire to focus on treatment of the tumor, rather than symptoms
3. Caused by the desire to please the medical and nursing staff
4. Caused by the expectation that pain is inevitable
5. Caused by use of the pain to follow the course of the disease

Fear of opioid drugs

1. Fear of adverse pharmacologic outcomes
2. Fear of addiction

Clinician-related Factors

Uncertainty about the role of opioid therapy

1. Patients cured or in remission
2. Patients with early or indolent disease

Undertreatment

1. Caused by failure of comprehensive assessment
2. Caused by deficiencies in knowledge of opioid therapy
3. Caused by overestimation of risks
risk of adverse pharmacologic outcomes
risk of addiction
4. Caused by regulatory policies

that patients, when talking to their doctors, either minimize their symptoms or do not report them at all. This behavior may relate to stoicism or to any of a number of responses that reflect the patient's adaptation to the cancer. These adaptive responses include the following: the desire to focus on the disease and its treatment, rather than on symptoms, during the typically short time available with the physician; the fear that voluble complaints may lead to less regard of the patient by the medical and nursing staff; the expectation that pain is an inevitable concomitant of the disease; the belief that pain must be experienced to monitor the status of the tumor; and the fear of opioid therapy.

Clinical observation suggests that the fear of opioid therapy is an important cause of the under-reporting of pain or noncompliance with opioid therapy. Many patients express concern about side effects, particularly mental clouding or sedation, and the experience of these effects after the initiation of therapy may confirm the patients' expectations and enhance resistance to therapy thereafter.

Even more compelling, however, is the widespread concern among patients that the medical use of opioid drugs will lead to addiction. Patients are exposed daily to lurid portrayals in the lay media of the drug abuse problem. The essential medical role for opioid drugs, and more importantly, the fundamental distinctions between pain patients who require opioids for symptom relief and street addicts who abuse drugs for psychotropic effects, are rarely discussed. Many patients perceive that there is no difference between the street addict and themselves except for exposure to a drug. Unless openly addressed and strongly refuted by the medical staff, this perception may add to the psychological burden of the patient or augment noncompliance.

Although clinical observation suggests that these patient-related factors contribute to the prevalence of

unrelieved cancer pain, the extent of this contribution, and the relationship of these factors to the determinants of clinician behavior, is unknown. It is likely that patient-related factors are less important causes of unrelieved cancer pain than clinician behavior.

Clinician-related Factors Contributing to Unrelieved Cancer Pain. Given the relatively low incidence of truly refractory pain, the evidence that optimal therapy with opioid drugs can provide relief to most patients, and the likelihood that patient noncompliance could be effectively addressed, it is likely that the number of patients with unrelieved pain could be greatly reduced if clinician undertreatment were reversed. In judging the benefits that could accrue from elimination of undertreatment, however, it must be appreciated that some ineffective prescribing is probably better understood as an "appropriate" response to a clinical situation rather than as true undertreatment. For example, patients predisposed to serious opioid toxicity may require a treatment strategy that minimizes opioid use. Likewise, some effort to limit opioid use may be appropriate when pain is related to a cancer that is in remission or cured and the pain syndrome presented by the patient is fundamentally similar to common chronic nonmalignant pain syndromes, wherein the use of opioid therapy remains controversial.²⁰ Improved outcome for such patients should not be expected from efforts to optimize prescribing practices, underscoring again the need to place in a broader context the changes necessary for effective cancer pain relief.

It is generally believed, however, that the proportion of cancer patients affected by such "appropriate" underprescribing is very small in comparison to the group for whom effective analgesic therapy is limited by clinician undertreatment. Undertreatment, in turn, may relate to several phenomena, including inadequate assessment, deficiencies in knowledge, overestimation of the risks associated with treatment, and the influence of regulatory policies.

Inadequate Assessment. The failure to perform a comprehensive assessment hinders treatment by providing inadequate information from which to evolve a therapeutic strategy. The importance of assessment is illustrated by a recent survey, which revealed that previously unrecognized lesions were discovered to be the cause of pain in more than 63% of patients referred to a cancer pain service.²¹

Deficiencies in Knowledge. Deficiencies in knowledge of pain management techniques comprise a second major cause of undertreatment. Professional training in pain management is meager, and that which exists is usually focused on the treatment of acute pain. Numerous surveys have confirmed that physicians and nurses commonly underestimate the doses required to relieve pain and overestimate the duration of effect after each dose.^{16,22,23} Guidelines for management of cancer pain are not readily accessible and are often unknown to clinicians.

Overestimation of Risk. Overestimation of the risks associated with chronic opioid therapy by prescribers and other health care professionals is another major cause of undertreatment. The perception of risk is based

on expectations about the likelihood and severity of adverse effects and the possibility of addiction. Adverse effects, such as respiratory depression and cognitive impairment, are a widespread concern in spite of a very large body of clinical experience indicating a high degree of safety with chronic opioid use. Drug administration is often unjustifiably limited in the expectation that an adverse effect will occur.

The fear of addiction can influence the treatment of any patient but appears to be most salient during opioid administration to patients with relatively early or indolent disease, particularly in younger patients. Opioids are abusable drugs, of course, and the actual risk of drug addiction or abuse during pain therapy must be appreciated to determine whether or not this concern is justified. If in fact there were a relatively high likelihood of opioid abuse in cancer patients administered these drugs for pain, the decision to withhold treatment from some patients on this basis would be appropriate.

Evaluation of the potential for opioid abuse in patients with cancer pain requires clarification of the terminology of dependence and abuse. Confusion about this terminology is widespread and impedes efforts to accurately assess the risk of addiction or abuse. For example, it has been observed repeatedly that clinicians often mislabel physical dependence as addiction and, in so doing, report a much higher rate of addiction than actually exists.

Physical dependence is a pharmacologic property of opioids and is defined by the occurrence of an abstinence syndrome after abrupt withdrawal of the opioid or administration of an antagonist.^{24,25} It may or may not exist in an addict and, although it is presumably very common in cancer patients receiving opioids chronically, it is not itself a clinical problem as long as the abstinence syndrome is not manifested.

In contrast, addiction is a psychological and behavioral syndrome characterized by *psychological* dependence and compulsive drug-related behaviors. Addicts ruminate about a drug and demonstrate aberrant (abuse) behaviors, such as hoarding, stealing, drug acquisition from nonmedical sources, and unsanctioned dose escalation. The prevalence of these addictive behaviors among medical patients receiving opioids for pain is vanishingly small.²⁶⁻²⁸ There are fundamental differences between the typical medical patient and the addict, which presumably underlie the differing effects of opioid administration in the two groups. For example, addicts report that opioids produce euphoria, whereas patients typically describe either dysphoria or no effect on mood.²⁹ Likewise, the psychological aberration of psychopathy, which is rare in the general population, is relatively common among addicts.³⁰

Thus, addiction is not a substantive issue in the management of cancer pain, and the fear of addiction should never be used to justify the withholding of opioid therapy from a patient with no history of opioid abuse. Even in substance abusers, addictive behaviors during medical therapy appear to be limited to a small subgroup of those persons actively abusing,³¹ and the withholding of therapy in response to this history is also unacceptable.³² Given this perspective, there can be no

justification for any regulation that reduces patient access to opioid drugs on the basis of the potential risk of addiction or any other adverse effect. Enlightened regulatory policy must recognize the medical necessity for opioids and other controlled prescription drugs, a view that has been affirmed by both the United Nations International Narcotics Control Board and the National Conference of Commissioners on Uniform State Laws.^{33,34}

THE IMPACT OF DRUG REGULATION ON THE MANAGEMENT OF CANCER PAIN

Although physicians recognize the need for prescription drug regulation to reduce the diversion and misuse of controlled substances,³⁵ there is a widespread perception that some regulatory policies hamper efforts to provide optimal care of patients with cancer pain. Consequently, the possibility that regulatory policies could exacerbate undertreatment by legitimate prescribers, and thereby increase the prevalence of unrelieved pain, must be carefully evaluated.

Regulators face a challenge in monitoring prescribers who treat patients with cancer pain because the standard clinical approach in these patients requires that controlled substances be used in a manner that could raise concern about polydrug abuse and addiction among those without expertise in this area of medicine. For example, patients with cancer pain are commonly prescribed more than one controlled prescription drug. Opioid-induced sedation is often treated with a psychostimulant, such as dextroamphetamine or methylphenidate, and benzodiazepines, which so concerned regulators in New York State that they placed the entire class within the multiple copy prescription program, are very often combined with opioids. Other controlled drugs, such as cannabinoids or barbiturates, are sometimes prescribed, and some patients receive more than one opioid. Furthermore, the dosing regimens used with these drugs, which commonly involve parenteral routes of administration, high escalating doses, and prolonged periods of chronic use, may also arouse concern.³⁶

Regulators without special training in these patterns of drug use may have difficulty distinguishing acceptable prescribing from misuse or diversion. Although some cases of diversion (eg, through "prescription mills") may be relatively clear-cut, the behavior of a prescriber who administers multiple controlled drugs at high doses to a smaller number of patients may be more difficult to evaluate. Unnecessary investigations of legitimate prescribers must be avoided but are likely unless regulators become more knowledgeable about the wide variety of pharmacologic approaches used to treat cancer pain patients.

Regulatory policies that are enforced without due regard for these imperatives of patient care may worsen undertreatment of cancer pain. Although research is needed to assess empirically the impact of regulation, it is apparent that the types of policies that could contribute to undertreatment include those policies that limit patient access to needed drugs and those policies that negatively influence prescribing behavior.

Policies That Limit Access to Controlled Prescription Drugs. Policies that limit access to needed drugs may directly induce underprescribing or place such burdens

on the patient or clinician that undertreatment results even if unintended. For example, some states do not allow the use of amphetamines, which are now widely accepted in the management of opioid-induced sedation. Others maintain a 120-dosage unit rule, which mandates that no more than 120 tablets can be prescribed to a patient at any one time. In states with the latter regulation, the high doses required by many patients with cancer pain necessitate very frequent prescription renewals, which can become onerous for both the patient and physician. Although less a problem, the 30-day maximum prescription period mandated by New York and other states can also become a problem for some patients, particularly those with chronic pain and stable disease who may live quite a distance from a cancer center.

A more subtle problem that may effectively limit access to controlled drugs by increasing the burden on the patient and physician is the need for strict adherence to guidelines for prescription writing. This problem is particularly notable when multiple copy prescriptions are needed to dispense controlled drugs. Patients may be told by their pharmacist that they must return to the physician for a new prescription because required information is missing or because extraneous marks appear on the form. Without condoning deficiencies in prescription writing, it is evident that this process increases the burden on both the patient and physician.

Policies That Negatively Influence Prescribing Behavior. Regulatory policies could also contribute to the undertreatment of cancer pain by adversely influencing prescribing behavior of clinicians. Although it is true that there are no statutory limitations on the use of controlled drugs to treat cancer patients, physicians are aware that their use of these agents is continually scrutinized by regulators. Physicians are not certain that regulators are knowledgeable about state-of-the-art prescribing practices, and since this knowledge is necessary to determine whether or not prescribing behavior is appropriate, there is concern that the legitimate use of controlled drugs will generate suspicion among those regulators monitoring this activity. This concern is increased by the lack of communication between regulators and clinicians. The standards used by regulators to determine the need for investigation or sanction are obscure; these standards do not appear in the medical literature, are issued from a site removed from the clinical arena, and may change without warning.

The adverse effect on prescribing practice that may be induced by the awareness of regulatory oversight can be conceptualized as part of a larger phenomenon, which is herein termed the "perceived risk of sanctions." Clinicians may limit prescribing of controlled substances in response to their perception that some personal risk accrues from the administration of these drugs to patients. The most prominent perceived risk is the possibility of investigation or sanction from state regulators. Other sources of risk may include hospital-based oversight committees and the implicit threat of malpractice litigation.

In addition to the awareness of regulatory scrutiny and the lack of certainty about the standards applied by

regulators, the "perceived risk of sanctions" is presumably sustained by the publicity accorded cases in which physicians who believed themselves to be legitimate prescribers came under investigation by regulators. These reports have appeared in both the lay press and the medical literature³⁷ and are common knowledge among physicians. Furthermore, the sanctions that may be brought against clinicians convicted of inappropriate or illicit prescribing, including loss of licensure or criminal prosecution, are clearly dire, and it is likely that this, too, enhances the perception of risk among clinicians who are not experts in pain management but would otherwise be willing to administer opioids and other controlled substances to their patients with cancer pain.

Multiple Copy (Triplicate) Prescription Programs. For clinicians in nine states, including New York State, the most visible reminder of the regulatory process is provided by the multiple copy prescription program. States with multiple copy prescription programs have recorded greater than 50% declines in the prescribing of the drugs included within the program.³⁸ Although proponents of these programs believe that this reduction reflects only illicit or inappropriate prescribing, there is no evidence to support this conclusion other than the lack of formal complaints from patients or clinicians. Many clinicians and patients do not find this argument credible, particularly in light of the undertreatment that currently exists. Furthermore, data from the federal Drug Abuse Warning Network (DAWN) do not confirm that these programs reduce prescription drug abuse,³⁹ and a Texas study suggests that legitimate prescribers respond to the program by reducing their use of Schedule II drugs and increasing their use of non-Schedule II drugs.⁴⁰

Given these observations, it is reasonable to suggest that the reduction in prescribing induced by the multiple copy prescription programs reflects a change in the behavior of legitimate clinicians who treat patients with medical disorders, like cancer pain, that are managed with controlled prescription drugs. It is likely that undertreatment is worsened by these programs. If so, an explanation for this effect may be found in the "perceived risk of sanctions," among other factors. The multiple copy prescription is a tangible reminder to the physician of the intense scrutiny that accompanies the prescription of these drugs, and awareness of this scrutiny may, as discussed previously, increase the clinician's perception that some personal risk accrues from the administration of these agents to patients. Other possible reasons for an effect on legitimate prescribing include the burden of paperwork, the cost, and the potential loss of privacy for patients.

Clinicians recognize the need for regulatory programs to reduce prescription drug abuse³⁵ and would not be opposed to one if its efficacy in reducing illicit activity had been clearly demonstrated and it would not impede medical practice. In the case of multiple copy prescription programs, the evidence of efficacy is unconvincing and there is reason to believe that the undertreatment of cancer pain may be worsened. As a result, cancer pain specialists join other opponents of these programs in concluding that these programs unjustifiably emphasize

regulation over patient care, and thereby skew the necessary balance that must exist between the two.

Implicit in the arguments that have been marshaled by those opposed to multiple copy prescription programs is the view that a statewide reduction in opioid prescribing, which has been adduced as evidence of effective drug abuse control by proponents of these programs, is an invalid indicator of illicit activities, and instead reflects overall levels of legitimate prescribing. This, in turn, suggests that clinician education designed to reverse undertreatment will probably lead to substantial increases in the monitored use of opioids and other controlled drugs. Such an occurrence has been demonstrated in Wisconsin, which has a model educational program in the management of cancer pain and has recorded a statewide increase in opioid prescribing concurrent with a decline in the indicators of abuse.⁴¹ This observation provides important contradictory evidence to the claims made by proponents of multiple copy prescription programs and documents that the therapeutic use of opioids will likely increase as the medical treatment of cancer pain improves.

CONCLUSION

Those who regulate controlled prescription drugs should recognize that cancer pain is unrelieved in a large proportion of patients. Among the many factors that may contribute to inadequate relief, undertreatment by clinicians is probably the most salient. Although prescription drug abuse is a problem and regulation is necessary, regulation without due regard for patient needs may worsen undertreatment by limiting access to necessary drugs or by negatively influencing prescribing practices. Regulators should be able to demonstrate that policies intended to stem illicit or inappropriate prescribing are effective and do not produce substantial adverse consequences for the care of patients. Many regulatory policies, such as the prohibition of drugs needed in clinical practice (eg, amphetamines) and the 120-dosage unit rule, do not meet this standard and thus skew the necessary balance between regulation and patient care.

Analyzed from this perspective, the implementation of multiple copy prescription programs cannot be supported. These programs reduce prescribing of opioids and other controlled drugs, but there is no evidence that this reduction is limited to illicit or inappropriate clinical behavior. Rather, it is reasonable to conclude on the basis of the data available that multiple copy prescription programs actually exacerbate undertreatment. As highly visible reminders of regulatory oversight, these programs may increase the perception on the part of the clinician that a risk of personal sanctions accompanies the use of controlled drugs.

These considerations suggest that better communication is needed between prescribers and regulators. A comprehensive review of federal and state drug regulations should identify those legal provisions that unnecessarily limit access to controlled prescription drugs or that negatively influence prescribing practices so that the provisions can be modified or revoked.

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Drug use and abuse in five US communities

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ABSTRACT. Data from the five-site Epidemiologic Catchment Area study (ECA), a probability sample of 18,571 adults, were used to describe the prevalence of drug abuse in the United States and to evaluate the hypothesis that multiple prescription regulations are effective in reducing drug abuse and drug diversion. The five sites surveyed were New Haven, Connecticut; Baltimore, Maryland; St. Louis, Missouri; Durham, North Carolina; and Los Angeles, California. The California triplicate prescription law was established in 1939 and is the longest continuously running triplicate prescription program in the country (Schedule II drugs). None of the other ECA sites had multiple prescription regulations in effect at the time the study was conducted. In general, the rates of drug use, abuse, and dependence were significantly higher in Los Angeles as compared with the other sites, both before and after controlling for sociodemographic differences. The proportion of users who go on to become abusers was consistent across sites (about 20%). The vast majority of those with a DSM-III diagnosis of abuse of prescription drugs reported that they obtained the drugs from a source other than their physician, suggesting that "diversion" of prescriptions from legal channels occurred at all sites. Limitations of the study design with respect to conclusions are discussed.

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It is widely recognized that drug abuse is a serious problem in the United States.¹ Although data based on high school students have frequently been reported, there have been relatively few national studies assessing the extent of the problem in adults.² This report has two goals: first, to provide physicians with an overview of the scope of the drug abuse problem in the United States. We present data on the rates of drug use and abuse in five United States communities, on the basis of data obtained from an epidemiologic study of over 18,000 adults.³

The second goal is to evaluate the evidence that multiple prescription regulations can substantially reduce drug abuse or diversion (or both) of prescription drugs for illegitimate purposes. The essence of such programs is the forwarding of copies of prescriptions to government enforcement and health organizations. In

the context of the question of multiple prescription reporting regulations, we focus on differences in rates of use and abuse of specific classes of drugs across study sites from the ECA study:³ New Haven, Connecticut; Baltimore, Maryland; St. Louis, Missouri; Durham, North Carolina; and Los Angeles, California. In doing so, we extend the analysis of Anthony and his colleagues, who have previously reported site differences for "any drug abuse-dependence."^{1,4}

Ideally, to understand the impact of triplicate prescription on the use and abuse of a particular class of regulated drugs, one should have longitudinal surveillance data based on probability samples of similar communities where triplicate prescription regulations have and have not been enacted. The data should be collected before the introduction of the regulation and then again after the regulations are in place. Community data are essential since persons are included on the basis of probability sampling rather than who happens to come for treatment. Samples based on patients coming for treatment are undoubtedly biased because only a small percentage of persons with a particular disorder or who use regulated medications actually come for treatment. Unfortunately, such ideal longitudinal surveillance data are not currently available.

In the absence of the ideal study, the data that we present are still relevant. California has had a triplicate prescription law for Schedule II drugs since 1939. In 1980, a large, community-based probability sample of adults designed to estimate the prevalence of psychiatric disorders, drug use, and drug abuse was initiated in five sites in the United States. One of these sites was Los Angeles, California. The data we present are limited by the fact that there were no such community sample data before 1939. However, when compared with other communities, which do not have triplicate prescriptions, the availability of data on drug use and abuse in Los Angeles and other sites constitutes an imperfect natural quasi-experiment. In this report, we describe site differences in rates of drug use, abuse, and diversion from legitimate (prescribed) use. Rates of alcohol use and abuse are presented for comparison.

METHODS

Overview. The ECA program was a collaborative project conducted by investigators at five sites between 1980 and 1983: New Haven, Connecticut; Baltimore, Maryland; St. Louis, Missouri; Durham, North Carolina; and Los Angeles, California.^{3,5} The primary purpose of

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the ECA was to determine prevalence rates of psychiatric and substance abuse disorders in adults ages 18 and over. The study methods have been described extensively elsewhere.³ Briefly, 18,571 household interviews were conducted using the Diagnostic Interview Schedule (DIS), a highly structured interview designed for use in epidemiologic studies employing lay interviewers. Computer algorithms were then applied to the data to construct psychiatric diagnoses and diagnoses of alcohol or drug abuse or dependence. Data are presented for drug and alcohol use, abuse, and dependence.

Drugs Assessed. The DIS was used to assess the use of illegal drugs and the misuse of prescription drugs with the purpose of obtaining American Psychiatric Association⁶ DSM-III diagnoses of abuse and/or dependence. Table I presents the classes of drugs covered in the interview schedule. It is not possible to distinguish within classes of drugs, for example, whether the use or abuse of tranquilizers involved Valium or Librium.

Drug Use. Subjects were handed a card with a list of drugs (Table I) and asked whether they had "ever used any drug on this list to get high, or without a prescription, or more than was prescribed, that is, on your own?" At four sites, subjects were then asked which of the drugs they had used more than five times in their lives. We refer to this as "simple" use because "ever used" was not asked in the DIS for specific drugs. At New Haven, however, subjects' responses to this question were not recorded for each drug and were thus not available for analysis.

Drug Abuse and Dependence. The rules for establishing DSM-III drug abuse or dependence diagnoses are complex. In general, the diagnosis of drug abuse requires a pattern of pathological use (use every day for two weeks or more, or use resulting in emotional problems) and evidence of impaired functioning (problems with family or friends, on the job or at school, or with police). The diagnosis of drug dependence requires self-reports of either tolerance (needed larger amounts to get an effect) or withdrawal (ever felt sick because medication was stopped or cut down). There are exceptions idiosyncratic to the DSM-III diagnostic system. For example, cocaine abuse, but not dependence, is diagnosed in DSM-III, and cannabis dependence requires tolerance or withdrawal plus pathological use or impaired functioning.

TABLE I. Epidemiologic Catchment Area Study: Description of Drug Classes Assessed by the DIS*

Cannabis: marijuana, hashish, pot, grass
Stimulants: amphetamines, uppers, speed
Barbiturates: barbiturates, downers, sleeping pills, Seconal, Quaaludes
Tranquilizers: tranquilizers, Valium, Librium, anxiolytics
Cocaine
Heroin
Opioids: codeine, Demerol, morphine, methadone, Darvon, opium
Hallucinogens: LSD, mescaline, peyote, psilocybin, DMT, PCP

*Drug Classes correspond to American Psychiatric Association DSM-III diagnostic abuse-dependence grouping. Data do not allow differentiation within classes.

In this report, we combine abuse and dependence into a single category reflecting a potentially serious clinical problem with the substance. The DIS also collects information on currency and recency; the data reported here are "lifetime."

Source of Drugs. If an individual reported abuse of or dependence on a prescription drug (eg, tranquilizers), he or she was asked whether the drug was obtained from a physician during the time he or she was having abuse-dependence problems, or from another (illicit) source.

Alcohol Use. At all five sites, persons were asked whether they had had enough alcohol on at least five occasions to get drunk. Although this history of alcohol use is certainly not comparable to using heroin more than five times, the question was chosen to compare "use rates" across the five sites.

Alcohol Abuse and Dependence. A DSM-III diagnosis of alcohol abuse requires a pattern of pathological use and impaired functioning. The DSM-III diagnosis of alcohol dependence requires tolerance or withdrawal plus pathological use or impaired functioning. As is the case for most drugs, one may meet the diagnosis for abuse but not dependence, dependence but not abuse, or both. Data are presented for the combined category abuse and/or dependence "ever in lifetime."

Statistical Analysis. The primary comparisons of interest were the Los Angeles site versus each of the other four ECA sites. All data are weighted to reflect the United States Census compositions of the communities and to correct for intentional oversampling (eg, of elderly subjects at New Haven and Hispanic subjects at Los Angeles). The rates of drug or alcohol use (Table II) and drug or alcohol abuse-dependence (Table III) are the unadjusted rates per 100 users' lifetimes by study site. The *p* values for significant differences in Tables II and III compare each of the other four sites to Los Angeles, with statistical controls for age, sex, social class, marital status, and racial differences using multivariate logistic regression techniques.⁷ Since statistical controls for other variables have been employed to determine site differences, apparently minor unadjusted differences were sometimes significant (eg, between Los Angeles and St. Louis for stimulant abuse-dependence; see Table III). The morbidity ratios reported in Table IV are the percentage of those persons reporting their having used a drug at least five times in a lifetime (ever gotten drunk in life) who go on to meet criteria for abuse-dependence. Statistical comparisons of percentages of subjects reporting that they obtained prescription drugs outside of medical treatment (Table V) are by χ^2 tests.

RESULTS

Drug and Alcohol Use. The use rates for five or more illicit uses of drugs were consistently higher in Los Angeles when compared with the other three sites (Table II, New Haven not available). Cannabis was the most frequently used drug, with lifetime rates ranging from 26.1/100 at Los Angeles to 15.1/100 at Durham, North Carolina. Other illegal drugs were also more frequently used at the Los Angeles site (Table II: heroin, cocaine, and hallucinogens). The use rates of prescrip-

TABLE II. Rates per 100 Subjects for "Simple Use" of Drugs, Five Times or More in Life, (Ever Gotten Drunk in Life)

	Cannabis	Stimulants	Barbiturates	Tranquilizers	Cocaine	Heroin	Opioids	Hallucinogens	Alcohol
New Haven	NA*	NA*	NA*	NA*	NA*	NA*	NA*	NA*	72.2
Baltimore	19.0 [†]	4.2 [†]	3.3 [†]	2.6 [†]	3.4 [†]	1.3 [†]	1.4 [†]	2.6 [†]	68.0 [†]
St. Louis	19.2 [†]	8.3 [†]	3.2 [†]	3.4 [†]	3.2 [†]	0.9 [†]	1.8 [†]	3.2 [†]	72.1 [†]
Durham	15.1 [†]	4.8 [†]	3.3 [†]	2.6 [†]	4.2 [†]	0.5 [†]	1.5 [†]	2.6 [†]	56.3 [†]
Los Angeles	26.1	10.3	7.1	5.6	11.3	1.5	3.0	6.6	73.8

*NA indicates data not available for New Haven (see text).

[†]Statistically significant differences between Los Angeles and other sites ($p < .05$), the primary hypothesis to be tested.

tion drugs were also highest in Los Angeles (opioids, stimulants, barbiturates, and tranquilizers). In particular, the rates of use of the three drug classes which included Schedule II regulated drugs (opioids, stimulants, and barbiturates) were highest in Los Angeles. To the extent that there were other differences apparent in the data, the rates of drug use were generally lowest in Durham, North Carolina, with Baltimore and St. Louis intermediate.

The rates per 100 subjects of "getting drunk ever in life" were similar for Los Angeles, New Haven, St. Louis, and Baltimore (ranging from 73.8/100 to 68.0/100). Given the large sample sizes, however, the rate of 73.8/100 for Los Angeles was statistically different from the other sites. The rate of 56.3/100 at Durham was substantively and statistically lower than for the other four sites.

Drug and Alcohol Abuse-Dependence. The pattern for drug use was repeated for drug abuse-dependence. The rates of drug abuse-dependence were consistently higher in Los Angeles (Table III). Cannabis was the most abused drug (~4 per 100 subjects across all sites). The low rates of cocaine use at all sites should be put in the context of the interview dates (1980–1983), which were before the introduction of "crack" cocaine. Classes of drugs containing Schedule II substances were most frequently abused at the Los Angeles site (stimulants, barbiturates, and opioids). Durham consistently reported the lowest rates of drug abuse-dependence, although not always so statistically.

Los Angeles (14.8%), Baltimore (13.7%), and St. Louis (15.5%) had similar and statistically identical rates of alcohol abuse-dependence. The rates in New Haven (11.3%) and Durham (9.1%) were significantly lower.

Morbidity Ratios. Morbidity ratios represent the percentage of "five times or more in life" users who go on to develop abuse or dependence (Table IV; "got drunk ever in life). In spite of the higher rates of use and abuse of drugs in Los Angeles, the morbidity ratios for

all classes of drugs were remarkably consistent with those for Baltimore and St. Louis. The percentage of users who go on to become drug abusers or drug-dependent is somewhat lower in Durham (information not available for New Haven).

The morbidity ratios for alcohol abuse-dependence produced similar results. Los Angeles (19.9%), Baltimore (19.4%), and St. Louis (21.3%) were highest, with Durham (15.9%) significantly lower.

Non-physician-Obtained Drugs in Abuse-Dependence. People meeting criteria for abuse-dependence of substances commonly prescribed by physicians were asked about the source of their drugs during the time they were having problems with withdrawal, tolerance, pathological use, or impaired functioning (Table V). Specifically, they were asked whether they were getting the drugs from their doctor (as prescribed) or from some other (illicit) source. The vast majority of DSM-III abusers-dependers reported that they had obtained the drugs *not* from their physician, but from a nonphysician source. The pattern of illegally obtained drugs was consistent across all sites with no evidence for a difference specific to Los Angeles (Table V).

DISCUSSION

The California triplicate prescription law was established in 1939 and is the longest continuously running triplicate prescription program in the country (Schedule II drugs). In general, the rates of drug use, abuse, and dependence were significantly higher in Los Angeles as compared with the other sites both before and after controlling for sociodemographic differences. The rates of users who go on to become abusers was consistent across all sites (~20% overall, with variation by drug class). The vast majority of subjects with a DSM-III diagnosis of prescription drug abuse or dependence reported that they obtained the drugs from a source other than their physician, suggesting that clinically important "diversion" of prescription drugs from legal channels occurred at all sites.

TABLE III. Rates per 100 Subjects Drug Abuse-Dependence

	Cannabis	Stimulants	Barbiturates	Tranquilizers	Cocaine	Heroin	Opioids	Hallucinogens	Alcohol
New Haven	4.3*	1.1*	0.5*	0.3*	0.1*	0.3*	0.2*	0.3	11.3*
Baltimore	4.1*	0.7*	0.6*	0.5	0.0*	0.5*	0.4*	0.1*	13.7
St. Louis	3.6*	2.0*	0.8*	0.7	0.1*	0.4*	0.3*	0.2*	15.5
Durham	3.1*	0.8*	0.6*	0.4	0.1*	0.2*	0.3*	0.3	9.1*
Los Angeles	4.9	2.1	1.6	0.7	0.6	0.6	0.7	0.5	14.8

*Statistically significant differences between Los Angeles and other sites ($p < .05$), the primary hypothesis to be tested.

TABLE IV. Morbidity Ratios: Percentage of Five Times in Life Users Who Go on to Abuse-Dependence

	Cannabis	Stimulants	Barbiturates	Tranquilizers	Cocaine	Heroin	Opioids	Hallucinogens	Alcohol*
New Haven	NA [†]	NA [†]	NA [†]	NA [†]	NA [†]	NA [†]	NA [†]	NA [†]	11.3
Baltimore	21.7 [‡]	17.8	20.9	22.3	0.0	40.9	30.2	4.4	19.4
St. Louis	19.0	24.0	33.1	26.4	1.5	43.6	18.8	5.4	21.3
Durham	20.3	17.7	19.1	19.7	1.9	33.8	22.6	12.6	15.9
Los Angeles	18.6	20.5	24.6	13.2	5.1	37.0	25.0	7.9	19.9

*Percentage of persons who ever got drunk in life who go on to abuse-dependence.

[†]NA indicates data for drugs not available at New Haven.

[‡]The morbidity rate of 21.7 for cannabis at Baltimore indicates that of the people who reported five or more uses in a lifetime (Table II), 21.7% went on to develop abuse or dependence.

The ECA study was not designed to answer questions about the effectiveness of multiple prescription regulations for reducing drug abuse and drug diversion to illegal channels. The ideal design would be to assign similar communities randomly to multiple prescription regulation (or not) and to measure drug abuse and diversion both before and after regulation. Although we have statistically controlled for sociodemographic differences across all sites in evaluating these results, Los Angeles doubtless differs in other unmeasured ways (eg, life-style, social norms, and attitudes). Furthermore, since we do not have a pre-1939 measure of drug abuse at any site, it is possible that abuse-dependence of drugs would be even higher in Los Angeles in the absence of a long history of triplicate prescription regulation.

The data in Table III suggest, however, that Los Angeles also had similar and higher rates of drug abuse-dependence for drugs outside the control of physicians or the legitimate pharmaceutical industry (eg, cannabis and cocaine). Although previous reports based on the ECA⁸ have suggested high rates of psychiatric disorders in drug abusers, the rates of psychiatric disorders are not generally higher at Los Angeles⁵; thus, another explanation for higher rates of drug abuse-dependence at Los Angeles is required.

We examined the percentage of users going on to abuse-dependence (morbidity ratios) both to examine the "process" of abuse-dependence and as a further test of the success of the triplicate prescription program in California. Even with the higher rates of drug abuse for drugs covered by triplicate prescription evident at Los Angeles, if the percentage of users going on to abuse-dependence were substantially lower than at other sites, the regulation program could still be considered successful. To illustrate, one might attempt an alcohol education program in a college setting and find that the percentage of students reporting alcohol abuse was still disturbingly high. However, if at the end of four years the percentage of those students using alcohol who went

on to become abusers was reduced relative to colleges without the intervention (lower morbidity ratio), the program could still be considered a success. Historically, that does not appear to be the case for Schedule II drugs at Los Angeles because the morbidity ratios at that site are similar to morbidity ratios at the other sites. Similar morbidity ratios may provide indirect evidence for the lack of a substantial impact of the California prescription regulation program on the reduction of drug abuse-dependence.

Questions about the sources of drugs for those subjects having problems with "prescription" drugs indicated that the vast majority obtained the drugs from someone other than a physician. This finding was true across all sites and across schedules of drugs. There was evidence of substantial diversion of prescription drugs at Los Angeles as well as at other sites. The message may be that we should not overestimate our ability to control the flow of prescription drugs through regulation of physicians in the face of individual compulsion to abuse.

As Anthony and Trinkoff⁴ have suggested, the factors effecting drug abuse are deceptively complex. A solution to the problem relying only on legal regulation is perhaps doomed to failure. The contrast between Durham, North Carolina, and the other sites might be instructive. Durham had the lowest rates of drug and alcohol abuse and generally lower morbidity ratios, suggesting that differences in rates of abuse are simply not a matter of "exposure" or availability. Although many of the Durham residents live in a small city, most are minutes from rural areas and differ in many other unmeasured ways (religion, values, social norms, and attitudes). Even in the absence of a multiple prescription regulation, the drug abuse problem is substantially less in Durham than at any other site. The lower rates at Durham strongly suggest the overwhelming influence of other social, environmental, or differentially distributed inherited factors in the etiology of drug abuse.

TABLE V. Source of Drugs: Percentage of Drug Abuse-Dependence Associated with Non-Physician Prescribed Source*

	New Haven	Baltimore	St. Louis	Durham	Los Angeles [†]
Barbiturates	90.5	93.5	94.9	100.0	100.0
Tranquilizers	66.5	88.4	93.9	95.3	94.8
Amphetamines	88.7	92.5	98.8	92.9	99.3
Opioids	89.6	100.0	100.0	100.0	96.6

*Persons reporting abuse or dependence were asked whether the problems occurred when taking the drug "on your own or under a doctor's prescription."

[†]New Haven, Baltimore, St. Louis, and Durham do not significantly differ from Los Angeles in the percentage reporting non-physician prescribed abuse for any of the four drug classes.

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The impact of the New York triplicate prescription program on the Hispanic community

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State initiatives such as triplicate prescription programs can have serious adverse effects on specific population groups when the requirements of those programs increase administrative or patient care work loads among already overburdened practitioners, violate cultural norms, and thus offend or intimidate patients, and impose additional cost burdens on economically disadvantaged persons. A recent survey suggests that the New York initiative to add benzodiazepines to the state's triplicate prescription program imposes all of those burdens on the state's sizable Hispanic community.

DESCRIPTION OF THE COMMUNITY

Approximately 25 million Hispanics, including an estimated 3.5 million illegal aliens, live in the United States today, constituting the fifth largest Spanish-speaking community in the world. That segment of the US population is expected to increase to 40 million by the year 2000, when Hispanics will be the largest minority group in the US.¹

The changing demographics of the Hispanic population play an important role in the development and implementation of public health policies aimed at improving health standards and access to health care for this community. A 1986 survey for the Robert Wood Johnson Foundation, for example, found that 30.1% of Hispanics have no regular source of health care and that this group is at higher risk for many diseases than the non-Hispanic population.²

Furthermore, unlike previous access surveys, which found Hispanics to be only slightly below the national average, the 1986 survey found a considerable deterioration in their situation. The percentage of Hispanics without a regular source of care was almost double that for non-Hispanic whites, and the percentage with a medical emergency was higher as well.²

That situation is further complicated by the Hispanic population's unequal access to almost every modality of health care, culturally based poor compliance with medical treatment, greater difficulties in paying for health care, and widespread lack of medical insurance²⁻⁴ (Table I).

DRUG ABUSE IN HISPANIC POPULATIONS

The 1982 National Drug and Alcoholism Treatment Utilization Survey suggests that Hispanics are almost three times as likely to be in treatment for a drug-abuse-related problem as non-Hispanic whites.³ In those surveys, Hispanic clients were more likely than white clients to report a primary problem with heroin and PCP. They also were more likely to report abuse of "other" drugs than white clients, with the most common drug in the "other" category reported as inhalants.^{3,5} Diversion and abuse of controlled drugs, on the other hand, are not as serious a problem among Hispanics as in some other population groups^{3,4} (Table II). Given that fact, it is ironic that the burden of certain programs to control prescription drug abuse, such as the New York benzodiazepine regulation, appears to fall more heavily on Hispanics than on other population groups.^{6,7}

IMPACT OF THE TRIPPLICATE PLAN ON HISPANIC PHYSICIANS

The previously cited high rate of illness in the Hispanic population creates a heavy burden for the approximately 24,000 Hispanic physicians practicing in the continental United States, who, largely because of language and cultural barriers, provide health care to more than 80% of the US Hispanic population. Thus, there is a ratio of approximately one physician for every 1,000

TABLE I. Indicators of Access to Health Care, by Race/Ethnicity, 1986

Key Indicators	White (%)	Black (%)	Hispanic (%)
Percentage of the population who:			
1. Do not have a regular source of health care	16.3	20.1	60.1
2. Do not have health insurance	7.7	10.1	21.7
3. Are in fair or poor health	10.6	15.3	19.4
4. Have a chronic or serious illness	20.4	21.1	15.8
5. Have not had a physician, other outpatient, or mental health visit within the past 12 months	31.6	37.4	38.0

Source: Survey of 10,130 US adults for the Robert Wood Johnson Foundation reported in *Special Report: Access to Health Care in the United States: Results of a 1986 Survey*. Princeton, New Jersey, Robert Wood Johnson Foundation, 1987, p 6.

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TABLE II. Persons Reporting any Illicit Drug Use in Lifetime, by Race/Ethnicity, 1988

Drug	White (%)	Black (%)	Hispanic (%)
Use of any illicit drug:	37.0	35.9	32.3
Marijuana	33.7	33.3	27.9
Cocaine	10.8	9.3	10.9
Crack	1.0	2.4	2.1
Inhalants	6.0	3.6	5.7
PCP	3.3	1.6	3.0
Heroin	0.8	2.3	1.1
Non-medical use of any prescription-type psychotherapeutic drug: ¹	12.7	7.7	9.4
Stimulants ²	8.0	2.6	5.2
Sedatives ³	3.8	2.3	2.5
Tranquilizers ⁴	5.2	3.1	3.3
Analgesics ⁵	5.4	4.1	4.4

¹For purposes of this survey, "non-medical use of any prescription-type psychotherapeutic drug" involves use that is either:

without a doctor's prescription, or
in greater amounts than prescribed, or
more often than prescribed, or
for any reasons other than that a doctor directed their use.

²Includes amphetamines and Preludin.

³Includes barbiturates, sleeping aids, and Seconal.

⁴Includes anti-anxiety agents such as Librium, Valium, Ativan, and meprobamate.

⁵Includes analgesics such as Darvon, Demerol, Percodan, and Tylenol with codeine.

Source: NHSDA: *Main Findings 1988*. Rockville, Md., National Institute on Drug Abuse, 1990.

Hispanic patients, more than twice the patients-to-physician ratio of the general population.⁴

Under those difficult conditions, the requirements of a triplicate prescription program can be expected to pose an additional burden on Hispanic physicians and patients.

PHYSICIAN/PATIENT SURVEY

To test that hypothesis, the Interamerican College of Physicians and Surgeons commissioned a survey of physicians and patients in the Hispanic community in New York State.⁶ The objective of the study was to determine the effects of the regulation, enacted in 1989 in New York State, that requires prescriptions for benzodiazepines to be written in triplicate. Areas of study included the following:

- Awareness of the triplicate prescription program
- Benzodiazepine prescribing patterns since 1989
- Reaction to the 1989 triplicate prescription program
- Alternative medications used
- Patient and physician satisfaction with current treatment

Telephone interviews with 302 Hispanic physicians were conducted in December 1990. Physicians interviewed represented more than 16 specialties, with the largest groups concentrated in internal medicine (28% of the survey respondents), psychiatry (16%), and family practice (13%). Among the survey respondents, 91% were men, half practiced in New York City, and 42% were engaged in solo practice. Respondents reported an average caseload of 81 patient visits per week and said

that about 18% of their patients are covered by the Medicaid program.⁶ Nearly nine in ten of the physicians surveyed (89%) indicated that they have a triplicate prescription pad, and almost all the physicians surveyed (98%) said that they were aware of the triplicate prescription regulation in effect in New York State. More than eight in ten (82%) of the physicians surveyed prescribe benzodiazepines. Of those, almost half (49%) indicated that their prescribing patterns have decreased since the 1989 triplicate prescription regulation was instituted. Forty-eight percent indicated that their prescribing has remained the same and 2% indicated an increase. Interestingly, specialists in internal medicine were the most likely to report a decrease in prescribing (63%), followed by family practitioners (56%). Psychiatrists reported the smallest decrease in prescribing (22%). None of the physicians reported that they were no longer prescribing benzodiazepines.

Among the physicians who indicated a decrease in their prescribing of benzodiazepines, the main reason cited was "Time consuming, too much paperwork" (86%), followed by "Concerned about government scrutiny" (25%), and "Patients have expressed concern/fears" (8%).

Almost six in ten (58%) of those physicians who indicated decreases in their prescribing of benzodiazepines said that they were substituting other medications or therapies. Specialists in internal medicine appear to be substituting most frequently (72%), followed by family physicians (50%), and psychiatrists (40%). A majority (81%) of those physicians in practice only one to two years indicated that they were substituting other medications or therapies (Fig 1).

When asked about choice of substitute therapy, more than half (56%) cited buspirone as the medication they are using to replace benzodiazepines, followed by diphenhydramine (18%), hydroxyzine (4%), doxepin (4%), and thioridazine (3%). Asked how satisfied they felt patients were with such substitute medications or therapies, seven in ten (69%) physicians indicated that their patients were "Somewhat satisfied;" 16% said they were "Not at all satisfied." Two thirds of the physicians indicated that they were "Somewhat satisfied" with other medications or therapies, and 18% were "Not at all satisfied".



Respondents 122

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FIGURE 1. Hispanic Physicians in New York State Substituting Medication, by Specialty.

Given those results, it is perhaps not surprising that physicians surveyed indicated that they were opposed not only to the inclusion of benzodiazepines in triplicate prescription programs, but also to the triplicate program in general (74%). Such opposition is consistent among all specialties and number of years in practice (Fig 2).

When Hispanic physicians were asked why they were opposed to the triplicate prescription program, the most frequent unprompted reasons cited were, "Too much paperwork" and "Government interference with professional medicine" (Table III).

When all physicians were asked to select those statements that best described their feelings about the triplicate prescription program, the statements selected most often were "Time consuming/too much paperwork," "It interferes with the practice of medicine," and "Raises concerns about patient confidentiality" (Table IV).

IMPACT OF TRIPPLICATE PRESCRIPTIONS ON HISPANIC PATIENTS

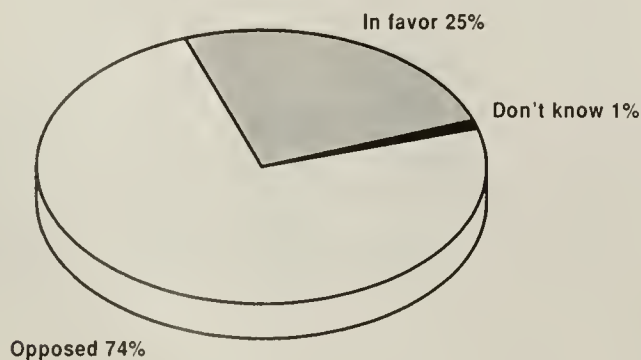
The survey also found that patients perceive the triplicate regulation to have a strong negative effect. Specifically, 103 patients completed written questionnaires in the first three months of 1991. These surveys were designed to elicit information about the following:

- Current and previous use of benzodiazepines
- Reasons for use
- Differences in prescribing of these medications
- Effects of regulation on the patient's lifestyle
- Awareness, knowledge, and opinion of the triplicate prescription program

Slightly more than six in ten respondents (61%) lived in the New York City area, whereas almost one quarter (24%) lived on Long Island. Almost nine in ten respondents (88.5%) indicated that they were currently taking one or more sedative/hypnotic agents as part of their medical treatment. Slightly more than one third (35.4%) indicated that they were currently taking diazepam, followed by alprazolam (19.8%), and lorazepam (18.8%).

More than eight in ten respondents (84.5%) indicated that they had previously taken one of the medications listed as part of their medical treatment. Again, diazepam was cited most frequently (33.8%), followed by flurazepam (15.5%).

Of those respondents who currently use a sedative-hypnotic, more than two-thirds (67.1%) cited "anxiety"



Respondents 302

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FIGURE 2. Physicians' Stance on New York Triplicate Prescription Program.

TABLE III. Physicians' Reasons Cited for Opposition to Triplicate Prescription Programs

Too much paperwork/too time consuming	30%
Government should not interfere with professional medicine	27%
It interferes with the practice of medicine	15%
Creates an unnecessary burden for doctors and patients	8%
Prevents certain patients from getting the medication they need	8%
An inconvenience	5%
Patients find it difficult to have prescription refilled	3%

as the reason, followed by "insomnia" (42.4%) and "stress/pressure" (3.5%). In that group, one quarter (25.0%) indicated that they had been taking the medication for five to six months, with an overall average of 3.81 months. Almost eight in ten (79.7%) cited "anxiety" as the reason, followed by "insomnia" (35.6%), "muscle spasm" (3.4%), and "other" (3.4%).

When respondents were asked why previously taken medications had been discontinued, reasons cited included the following: "I didn't need the medication anymore" (43.9%), followed by "I was put on another medication" (38.6%).

One quarter (24.8%) of respondents indicated that there was a difference in the way the medicine is/was prescribed compared with the way other medications are prescribed to themselves or their families. Furthermore, more than nine in ten (92.9%) cited "Extra forms for state use required/triplicate" as the difference, followed by "More work for doctors and pharmacists" (7.1%), and "I have to pay more for health care costs" (7.1%).

Almost four in ten respondents (39.6%) indicated that they see or had seen their physician once a month for the problem for which they take/took the medication. More than three quarters of respondents (77.2%) indicated that there has been no change in the frequency of visits to their physician from any previous time. Some 16.8% visit their doctor less frequently than before and 5.9% indicated an increase in doctors' visits.

Of those respondents who visit the doctor more frequently than previously, all indicated that the reason was "Because of triplicate forms, doctor can only prescribe a certain amount." Two thirds of that group felt that the increase in visits "Made no difference," whereas one third felt that this increase in visits was "Bad" because "I pay more for transportation, health care; need to arrange more" or because "It is too time consuming and costs me more money than before."

Of those respondents who visit the doctor less frequently than before, over half (57.1%) indicated that

TABLE IV. Statements Describing All Physicians' Feelings About Triplicate Prescription Programs

Time consuming/too much paperwork	78%
It interferes with the practice of medicine	56%
Raises concerns about patient confidentiality	32%
Will reduce illicit use	31%
Raises concerns about physicians being singled out	28%
Prevents inappropriate prescribing	27%
No problems experienced	14%
More physician visits allow for better overall care	12%

this was because “My treatment doesn’t necessitate as many visits,” followed by “I am no longer taking this medication,” (35.7%) and “It is too much trouble to go” (7.1%).

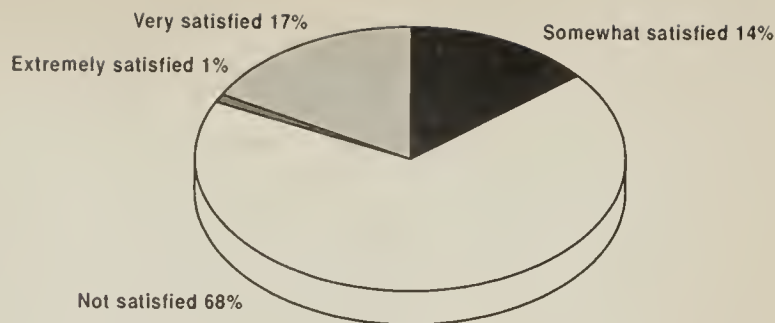
Among respondents who were aware of the triplicate program, over half expressed concern that the program creates a government record documenting their use of benzodiazepines. Almost six in ten respondents strongly agreed with the statement “The triplicate prescription system makes it harder for me to get my medication.” More than four in ten respondents strongly agreed with the statement “The triplicate prescription system causes me to visit my doctor more often.”

More than half of respondents strongly agreed with the statement “The triplicate prescription system causes me to have to refill my prescription more often.” Almost six in ten respondents strongly agreed with the statement “The triplicate prescription system reduces the chance that my medical information remains confidential.” Again, almost half of the respondents strongly agreed with the statement “The triplicate prescription system increases my health care expenses.” Therefore, it is not surprising that 68% of the Hispanic patients surveyed were not satisfied with the triplicate prescription program, and another 14% were only “somewhat satisfied” (Fig 3).

CONCLUSION

There is no doubt that diversion of controlled substances occurs in the United States. That diversion must be addressed but not exaggerated. The consensus among Hispanic physicians is that diversion problems should be solved not by monitoring those who use these drugs for legitimate medical purposes, but rather through law enforcement that addresses and eliminates the sources of diversion.⁸

The Interamerican College of Physicians and Surgeons, a national organization representing Hispanic physicians, is actively involved in a number of federal programs aimed at reducing the abuse of alcohol and



Respondents 103

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FIGURE 3. Hispanic Patients' Stance on the New York Triplicate Prescription Program

drugs and promoting the early treatment of drug abusers.⁹ However, a majority of Hispanic physicians who participated in a recent survey believe that concern about drug abuse must not interfere with the appropriate medical use of psychoactive drugs. They further believe that the New York triplicate prescription program imposes formidable barriers to high-quality patient care because the program is incompatible with certain cultural and economic aspects of life in the Hispanic community.

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Multiple copy prescription programs and alternative monitoring programs: Cost issues

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The debate between proponents and opponents of triplicate prescription programs often focuses on economic issues, specifically the alleged relative taxpayer savings and costs of these programs versus those of alternative methods of monitoring and investigating prescription drug diversion and abuse. Proponents report that access to data derived from triplicate prescription programs increases the efficiency of investigations and prosecutions of fraudulent pharmacists or prescribers. Opponents point to the large amount of money spent collecting the data.

REPORTED REDUCTIONS IN GOVERNMENT EXPENDITURES

Recently, proponents of triplicate programs have claimed substantial reductions in expenditures for benzodiazepines by New York State Medicaid and state-funded health insurance after benzodiazepines were added to New York State's triplicate prescription program.¹ Additional savings, resulting from decreases in benzodiazepine-induced hospitalizations, have also been claimed.

John Eadie, of the New York State Department of Health, which administers the New York State triplicate program, reported that in the year after benzodiazepines were added to the program, New York State Medicaid saved \$15 million; the State's Elderly Pharmaceutical Insurance Coverage (EPIC) program saved \$2 million; and the Empire Plan, the state and local government employees' insurance program, saved \$1 million in benzodiazepine expenditures.¹ New York State triplicate officials also cite \$10 million in expenditures for hip fractures and suggest that benzodiazepine-related fractures account for some substantial portion of these expenditures.

The New York State Department of Health also reports that the addition of benzodiazepines to the triplicate program resulted in a 55% decrease in Medicaid claims for benzodiazepines and a 27% decrease in the number of prescriptions for benzodiazepines written for Empire Plan members.² The number of participants in the EPIC program submitting claims for benzodiazepines decreased by 23%.

During the 1990 Congressional budget debate, Congressman Fortney (Pete) Stark of California introduced a measure that would require all states to have a triplicate prescription program for all controlled drugs under penalty of loss of Medicaid funding.³ Congressman Stark states that the savings that would accrue from having these programs nationwide would be \$1 billion annually, presumably from reduced Medicaid and Medicare expenditures. Although no detailed breakdown was provided, the estimates appear to be based on New York State's claims history.

EVALUATION OF SAVINGS ASSUMPTIONS

In their review of policy experiments by state drug benefits programs, Soumerai and Ross-Degnan⁴ point out that legislators often assume that savings from drug policy changes are equal to the decrease in the dollar value of prescriptions for the targeted drug and assume "(1) that physicians will not substitute other prescription or nonprescription treatments for perceived health problems; (2) that the lack of access to medications will not exacerbate both psychological and physical illnesses, prompting some patients to seek more intensive care; and (3) that patients will not purchase nonreimbursed drugs out of pocket."

Substitution of Alternative Drugs. The report of cost savings to New York State accruing from the addition of benzodiazepines to the triplicate prescription program offers a good opportunity for public policy makers to apply Soumerai and Ross-Degnan's caution. Although no calculation was made of increases in expenditures as the result of substitution of alternative drugs not included in the program, the New York State Department of Health reported that there were increases in prescriptions written for drugs that may be substituted for benzodiazepines (barbiturates, chloral hydrate, hydroxyzine, meprobamate, and buspirone).⁵ The department reported a decrease per quarter of 215,497 benzodiazepine prescriptions written under the New York State Medicaid program during the first half of 1989 compared with the average number of Medicaid prescriptions written during the same period in 1988. At the same time, Medicaid data showed an increase of 44,580 prescriptions written for nonbenzodiazepine sedative-hypnotics. Similarly, state-employee-paid benzodiazepine prescriptions decreased by 12,207 per quarter during the first six months of 1989, compared with a

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2,700 increase in prescriptions for selected nonbenzodiazepine sedative-hypnotics.

Many of the hypnotics prescribed as alternatives to benzodiazepines are not covered by New York State Medicaid, and therefore the use of these other medications by Medicaid recipients could not be measured by the Department of Health. If prescribers substituted drugs that were not reimbursable by Medicaid, these drugs would have to be paid for by the Medicaid recipients themselves without reimbursement. Although this substitution may represent a savings to the state, it is at the expense of a group ill able to afford the purchase. In addition, the reports of these Medicaid savings fail to take into account that only 50% of Medicaid expenditures are paid by the state; the balance is paid by the federal government, that is, the taxpayer.

The effect of a triplicate program on prescribing of Schedule II drugs was studied at an outpatient pharmacy serving 1,000 physicians in a large Texas medical center.⁶ In the first year of the triplicate program, the number of Schedule II prescriptions dispensed by this pharmacy decreased 60%, whereas the total number of prescriptions increased 13%. At the same time, prescribing of non-Schedule II narcotic analgesics underwent a sharp increase as compared with other drugs. For example, acetaminophen with codeine (30 mg) increased 26%, and acetaminophen with codeine (60 mg) increased 48%, whereas the non-scheduled analgesic zomepirac increased by 55%.

The Wisconsin Medicaid program eliminated reimbursement for propoxyphene napsylate (propoxyphene HCl remained reimbursable) to reduce program expenditures. However, an examination of the results of this change revealed that whereas propoxyphene reimbursement expenditures decreased by about \$500,000 per year, overall Medicaid reimbursement expenditures for analgesics increased.⁷ The failure of the Medicaid program to save money by changing its reimbursement policy appeared to be related to practitioners substituting more expensive reimbursable analgesics for propoxyphene, as evidenced by a \$400,000 increase in reimbursement expenditures for nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly more expensive than scheduled analgesics. The average amount paid per prescription for scheduled analgesics ranged from \$6.62 to \$11.41 compared with a range of \$19.69 to \$24.48 for NSAIDs.

Hospitalizations. Advocates of triplicate prescription programs point to decreases in rates of hospitalization as a positive outcome of the programs. A study of Michigan Medicaid recipients examined the relationship between hospitalizations for hip fractures and psychotropic drug use.⁸ There was an increase in the relative risk of hip fracture of 1.8 for recipients receiving a benzodiazepine with a long elimination half-life. Similar relative risks were found for antipsychotics and tricyclic antidepressants, both of which are nonscheduled drug classes. However, a later study by these same researchers examined relative risk of hip fracture by recipients using a benzodiazepine with a short elimination half-life (eg, triazolam) as well as those with a long elimination half-life (eg, flurazepam).⁹ They found a relative risk of

hip fracture of 1.7 for those taking benzodiazepines with a long elimination half-life, but a relative risk of only 1.1 for benzodiazepines with short elimination half-life. In clinical use, the latter have replaced a significant portion of the benzodiazepines with a long elimination half-life since the early 1980s, when the initial study was done.^{10,11}

TRIPPLICATE PRESCRIPTION PROGRAM COSTS

Creation of new drug data bases to target prescription drug abuse or diversion adds significantly to public and practitioner cost. The US Drug Enforcement Administration (DEA) has reported that the average administrative cost per triplicate prescription is between \$0.58 and \$0.68.¹² A more recent analysis by the California Department of Justice, accompanying a request to expand current triplicate activities to include benzodiazepines, reported an average administrative cost per prescription of \$1.00.¹³ The analysis projected an annual administrative cost of nearly \$6 million to add benzodiazepines to the California program. New York reports a total triplicate prescription cost of \$1.4 million for 1990.¹

The costs to practitioners and pharmacists of managing the additional paperwork have not been evaluated. However, these costs are not insignificant. They include professional and clerical labor costs for managing the flow of paper to the triplicate program, for ordering of forms, for filing of completed prescriptions, and for preparing forms for submission to the state triplicate agency. In addition, most states charge for each state-generated prescription blank (eg, New York charges \$0.25).

ALTERNATIVE MONITORING PROGRAMS

Critics of triplicate prescription programs point to existing programs that are far less expensive to develop and maintain and are more efficient at targeting inappropriate or fraudulent activities by practitioners, pharmacies, and patients. There are state and federal data bases in place that have been used to monitor prescription drug diversion.

Some of these data bases were created for the purpose of monitoring diversion, and some were created for other purposes. No additional expenditures are needed because the information has already been collected. The following approaches have been used by state authorities and others to target drug diversion and for educational interventions.

Automation of Reports and Consolidated Orders Systems (ARCOS). ARCOS, a computerized system maintained by the DEA, uses records of purchases of Schedule II drugs and Schedule III narcotics to identify registrants who buy large quantities or unusual combinations of scheduled drugs. As required by law, ARCOS reports are available to states on a quarterly basis from the DEA specifically to aid states in identifying and controlling sources of diversion.¹⁴ There is no charge to states for the reports.

Some states have used these reports to target investigations of pharmacies and other purchasers of covered drugs.^{15,16} Wisconsin used ARCOS data to identify purchasers of large quantities of amphetamines. Investigation by the Wisconsin Pharmacy Examining Board

inspectors, armed with exceptional-purchase information, identified eight prescribers who accounted for 88% of the 10,212 prescriptions for amphetamines audited. Two of these prescribers were convicted in federal court of unlawful distribution of controlled substances without a legitimate medical purpose. The Wisconsin Medical Examining Board subsequently considered as unprofessional conduct the prescribing or dispensing of amphetamines for any purpose other than five limited clinical indications. As a result of these investigations and convictions and a number of other amphetamine-related activities coordinated by the Wisconsin Controlled Substances Board (CSB), amphetamine purchases in Wisconsin decreased by 97%. The Wisconsin CSB reported no corresponding increase in Schedule III or Schedule IV stimulant-anorectics.

The American Medical Association (AMA) system, the Prescription Abuse Data Synthesis (PADS) program, assists states in identifying potential diversion and uses several data bases, including ARCOS, state crime laboratory reports, and Medicaid claims data to identify potential diversion targets.¹⁷ The primary limitation of ARCOS is that it can identify the purchaser of Schedule II drugs and Schedule III analgesics but cannot identify the prescriber unless that person is also the purchaser.

Medicaid Claims Data. Medicaid claims data have been used by Wisconsin and a number of states using PADS to identify recipients, pharmacists, and physicians who are involved in abuse or diversion of controlled drugs.¹⁸ The Medicaid data are by-products of claims payment and are organized in the computerized Medicaid Management Information System (MMIS), which permits sophisticated retrieval of exceptional drug use. Although MMIS data are limited to services reimbursed by Medicaid (18% of all outpatient drugs), the data have several advantages: The information is collected during claims payment, so no additional expense is involved in collecting data; Medicaid reimburses for all schedules of drugs, not just Schedule II, permitting review of abuse of all scheduled drugs; diagnostic information, available in the claims data base of Medicaid, can be used effectively to target those prescribers, pharmacies, and patients who may be using controlled drugs inappropriately, without interfering with the drug use of those with legitimate needs (eg, cancer patients).

Most states use Medicaid data to identify recipients who have been "shopping" by going to several prescribers and pharmacies to secure large amounts of controlled drugs. These recipients may then be restricted to a single pharmacy or physician to control Medicaid-reimbursed diversion. Wisconsin Medicaid also provides detailed patient drug-use histories to law enforcement and regulatory agencies when practitioners, pharmacies, or recipients appear to be overusing drugs.¹⁸

The General Accounting Office (GAO) reviewed four state Medicaid agencies, including Wisconsin and New York, to see how MMIS could be used to monitor diversion.¹⁹ The GAO noted that MMIS is the largest data base on prescribing and dispensing of controlled substances in a state. Aberrant patterns of use can be used to pinpoint problems not limited to Medicaid programs. The GAO has suggested that the Department

of Health and Human Services (HHS) and the Department of Justice test the usefulness of providing MMIS data to regulatory, licensing, and law enforcement agencies for identifying sources of drug diversion.

The Office of the Inspector General (OIG) of HHS has developed the Medicaid Abusable Drug Audit System (MADAS) computer software that states can use in conjunction with Medicaid claims data to identify recipients, pharmacies, and prescribers who appear to be exceptional users of controlled drugs.²⁰ The OIG reports that the system has been used successfully in at least three states (New Mexico, Maryland, Pennsylvania) to target drug diversion.

Drug Utilization Review. Medicaid agencies, health maintenance organizations, insurance companies, and others have been using claims data to perform prescription drug use review (DUR).²¹ DUR is a physician-education program designed to ensure appropriate drug use, to identify potential adverse drug reactions, and to manage drug costs. The Omnibus Budget Reconciliation Act of 1990 requires all state Medicaid programs to implement a DUR program by January 1, 1993; it must identify patterns of fraud, abuse, gross overuse or underuse, and inappropriate or unnecessary drug use.

DUR has all the advantages previously mentioned for Medicaid claims data. Because inappropriate controlled-drug use is often attributable to physicians with outdated prescribing habits and not to fraudulent prescribers, education is often a more fitting intervention. The major disadvantage of DUR based on claims data is that it is restricted to the populations covered by Medicaid or insurance programs.

Electronic Data Transmission. Ninety percent of all prescriptions are now dispensed by pharmacies using computers. These computers are often tied to central data bases via a "black box" or a third-party computer vendor that provides the communications link from the pharmacy's computer to a central data base. Increasingly, pharmacists are submitting drug claims directly to claims processors via computer. The pharmacist is thus able to check potential drug interactions and can be alerted instantaneously, before dispensing the drug, to a patient who has recently received the same drug from another pharmacy.

Equipping each pharmacy with the link to the central depository will require a significant expenditure. To encourage state Medicaid agencies to adopt computer networks for claims processing and DUR, the federal government is presently paying 90% of the cost of implementation.

The pharmacist also could use electronic data transmission (EDT) networks to report controlled-drug prescribing information daily or weekly to the monitoring agencies. Once the initial investment in the technology is made, EDT of controlled substances dispensed can be done at a modest cost, compared with triplicate prescription programs—which have been estimated to require \$1 per prescription just to have the controlled-substance prescription data entered. In fact, advances in computer technology for pharmacies will make paper-based systems such as triplicate prescriptions antiquated. Manual

re-entry of data that is already in a pharmacy's computer is a very inefficient means of collecting the data.

Oklahoma is in the process of implementing a program that uses EDT systems to report Schedule II prescriptions to a state agency charged with the responsibility for monitoring drug diversion.²² Other states are considering similar programs. However, like triplicate prescription programs, the EDT technology will not allay the concerns of those who feel that central collection of these data risks breach of confidentiality.

CONCLUSION

The triplicate prescription program has created a demand for more costly substitute drugs, which does not help the Medicaid recipient or the Medicaid system itself, and some alternative drugs are not covered or reimbursable by Medicaid. An additional cost is one that cannot be measured in dollars—the loss of confidentiality, which has provoked resistance to triplicate programs by physicians, pharmacists, and patients.

To create a new data base from triplicate prescription information when so many alternative systems are already in place is contrary to one of the stated goals of the triplicate prescription program—to save money for the state. Existing programs—ARCOS, MMIS, DUR, and EDT—are currently in place to provide the same data as a triplicate program and at a lower cost.

It seems clear from these observations that states should test programs that make use of existing data before embarking on the development of expensive programs that rely on collection of new data; that rigorous evaluations by disinterested parties should be made of triplicate prescription programs and other controlled drug monitoring programs; and that evaluations of these programs should include analyses of all health care costs (not just targeted drug costs) and examination of quality-of-life issues.

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Prevalence of prescription drug abuse: Data from the National Institute on Drug Abuse

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There is much concern over prescription drug abuse in this country and a perception that psychotherapeutic agents are often diverted. Among the programs instituted to address prescription drug abuse and diversion are multiple copy prescription programs, frequently referred to as triplicate programs. Data from the Drug Abuse Warning Network (DAWN), which is operated by the National Institute on Drug Abuse (NIDA), have been used by both proponents and opponents of triplicate programs to support their cases.^{1,2}

In spite of the controversy over triplicate programs, general agreement exists that there has been an approximate 50% reduction in the number of prescriptions for licit psychotherapeutic agents in states where triplicate laws took effect. Law enforcement agencies, including the Drug Enforcement Administration, believe that the decreases reflect reductions in overprescribing, but physicians and other health officials argue that triplicates have a "chilling" effect on medical practice and that both anxiety and pain are undertreated in the United States.

This paper uses data from the National Household Survey on Drug Abuse (NHSDA) and DAWN to assess the current prevalence of the abuse of licit psychotherapeutic agents and the consequences associated with such abuse. The differences in the populations whose motivation for taking drugs is dependence/psychic effects vs suicide are also discussed. The remainder of this paper focuses on data from DAWN. Although both New York City and Buffalo are in DAWN, this paper focuses on data from New York City. This paper does not attempt to use DAWN data to support or refute the efficacy of triplicate programs.

NATIONAL HOUSEHOLD SURVEY ON DRUG ABUSE

The NHSDA, conducted since 1971, has been sponsored by NIDA since 1974. The 1990 survey represents the tenth study in the series. Information on drug use, including the nonmedical use of licit psychotherapeutic agents, is collected from a national probability sample of households in the contiguous United States. In 1990, 9,259 interviews were completed between March 12 and June 30, with a response rate of 82%. The data are based on self-reports and do not include the transient and

incarcerated populations. Thus, these estimates of drug use may be conservative.

Drug abuse is a significant problem in this country. It is routinely cited as one of the top three problems facing the nation. The magnitude is enormous: 37% of the household population of the United States has tried drugs. The good news is that drug use is decreasing. The past-month use (current use) of marijuana has been decreasing for a number of years (Table I). In the last three years, past-month use of cocaine has decreased from a peak of 5.8 million in 1985 to an estimated 1.6 to 1.7 million current (past-month) users in 1990.

Although the abuse of cocaine has received enormous publicity, we must recognize that the nonmedical use of licit psychotherapeutic agents is not an insignificant problem. While the nonmedical use of any of these drugs (eg, tranquilizers and analgesics) in the past month is less than 1%, collectively, the nonmedical use of these drugs represents 1.4% of the household population, or almost 3 million people (Table II). However, between 1988 and 1990 there was a decrease in past-year use of these drugs, while past-month use remained stable at less than 2%. The trend in past-year use of licit psychotherapeutic agents shows significant decreases in the nonmedical use of stimulants, sedatives, and tranquilizers but no change for analgesics (Table III). Past-year cocaine users are polydrug users; they have higher rates of current alcohol, stimulant, and tranquilizer use than those who have not used cocaine in the past year (Table IV). There is a significant abuse problem, a polydrug problem, but a problem that appears to be ameliorating.

DRUG ABUSE WARNING NETWORK

DAWN collects data on drug-abuse-related emergency episodes from 21 cities plus a national panel.

TABLE I. Rates of Past-month Drug Use, Age 12 and Older (% of households surveyed)

	1977 (%)	1979 (%)	1982 (%)	1985 (%)	1988 (%)	1990 (%)
Any Illicit Use	NA*	13.7	12.3	12.1	7.3	6.4 [†]
Marijuana	9.5	12.7	11.0	9.4	5.9	5.1 [‡]
Cocaine	1.0	2.4	2.3	2.9	1.5	0.8 ^{‡‡}

*NA indicates not available.

[†]Difference between 1985 and 1990 is statistically significant at the .05 level.

[‡]Difference between 1988 and 1990 is statistically significant at the .05 level.

Source: NHSDA.

From the Office of the Director, National Institute on Drug Abuse.

Address correspondence to Dr Adams, Gordon S. Black Corporation, 135 Corporate Woods, Rochester, NY 14623-1457.

TABLE II. Trends in Nonmedical Use of Any Psychotherapeutic Agents, 1988–1990

	1988		1990	
	No.*	Percentage	No.*	Percentage
Lifetime	23,536	11.9	24,025	11.9
Past Year	11,399	5.7	8,567†	4.3†
Past Month	3,393	1.7	2,858	1.4

*In 1,000s.

†Significant at .05 level.

Source: NHSDA.

Since 1986, NIDA has been recruiting the facilities required to convert DAWN to a statistical sample. In 1989, 770 facilities reported to DAWN, of which 641 are part of the DAWN sample. The response rate from the hospitals was approximately 79%. Data are collected on the drugs used, demographics, reason for taking substances, reason for present contact, source of substance, etc. DAWN data are often cited to support increases or decreases in drug use. They are not a measure of use but a measure of consequences, although they are often misinterpreted as a measure of prevalence.

The ranking of the top ten drugs mentioned in DAWN in 1989 (Table V) and the percentage of the mentions that represent suicide or suicide gestures provide important data because “Reason for Taking Substance” is collected as part of DAWN, and in most “drug abuse” cases the motivation for taking the substance is not suicide but rather either dependence or psychic effect (Table V).

It has been the position of this writer that suicide does not reflect drug diversion.³ Rather, suicidal persons usually take drugs that are available in their homes. That is why aspirin and acetaminophen are so often used, and because of their use in suicide attempts, they are ranked fifth and sixth in DAWN. Although diazepam is eighth and alprazolam is tenth, a high proportion of these mentions are also associated with suicide attempts/gestures. In contrast, those drugs associated with street use (eg, heroin and PCP) have a very low proportion of mentions associated with suicide attempts/gestures.

In DAWN, drugs used in suicide attempts/gestures are usually licitly obtained prescriptions or over-the-counter drugs, often used in combination, especially with alcohol. There is no evidence, nor to this writer’s knowledge is it contended, that people are diverting drugs to attempt suicide. The impact of excluding

TABLE III. Trends in Past-Year Use of Licit Psychotherapeutic Agents, 1988–1990

	1988		1990	
	No.*	Percentage	No.*	Percentage
Stimulants	4,957	2.5	3,109†	1.5†
Sedatives	3,099	1.6	2,233	1.1†
Tranquilizers	4,407	2.2	2,538	1.3**
Analgesics	5,342	2.7	4,999	2.5

*In 1,000s.

†Significant at .01 level.

‡Significant at .05 level.

**Significant at .001 level.

Source: NHSDA.

TABLE IV. Current Use of Other Drugs Among Past-Year Cocaine Users and Non-Cocaine Users

	Past-Year Cocaine Use	
	Yes	No
Alcohol	92	67
Cigarettes	60	36
Marijuana	71	7
Stimulants	13	1
Tranquilizers	9	1

Source: 1985 NHSDA.

suicide attempts/gestures from cases is dramatic. For example, if only dependence/psychic effects were included in the number of alprazolam cases in 1989, the number would drop from 3,567 to 781. Therefore, suicide cases should not be considered when assessing the impact of triplicate prescription or other drug diversion control measures.

The data from the five-year period from 1985 to 1989 from consistently reporting hospitals (that is, hospitals that reported at least 90% of the time, so that any change is not due to a change in the number of hospitals reporting) show that DAWN mentions of benzodiazepines decreased approximately 19%, and narcotic analgesics decreased by about 13%, although until 1989 the pattern for analgesics was stable (Table VI). Overall, there has been a general decrease in the consequences associated with the licit psychotherapeutic agents. Closer examination reveals differing patterns, ranging from stability (eg, antidepressants) to continuous declines (eg, barbiturate sedatives). When “All Other Mentions” are excluded, there is a 15% decline in DAWN mentions for the licit psychotherapeutics between 1985 and 1989.

In the DAWN system the majority of cases are associated with overdoses, unexpected reactions, and chronic effects. Emergency room visits associated with controlled prescription drugs, which represent about 21% of the DAWN cases, decreased about 20% between 1985 and 1989 (Table VII). During this time, the overall number of DAWN cases generally increased. DAWN data show that there has been an overall decrease in hospital visits related to Schedule II drugs in both triplicate and non-triplicate states (Table VIII). (Detroit is treated separately because Michigan implemented triplicate prescription in mid-1989.)

TABLE V. Drugs Most Often Reported in the Drug Abuse Warning Network, 1989

	Total Mentions	Rank	Percentage Suicide
Cocaine	61,665	1	4.9
Alcohol-in-Combination	47,735	2	25.4
Heroin/Morphine	20,566	3	3.1
Marijuana/Hashish	9,867	4	5.4
Acetaminophen	6,456	5	82.7
Aspirin	5,048	6	53.4
PCP/PCP Combinations	4,899	7	4.2
Diazepam	4,874	8	55.3
Ibuprofen	3,944	9	
Alprazolam	3,567	10	59.6

TABLE VI. Emergency Room Data: Number of Mentions of Selected Drug Groups According to Year, 1985–1989*

	1985	1986	1987	1988	1989
Tranquilizers and Benzodiazepines	13,279	12,926	12,959	12,062	10,776
Narcotic Analgesics	5,222	5,336	5,366	5,051	4,529
Nonnarcotic Analgesics	966	921	957	818	753
Barbiturate Sedatives	1,916	1,611	1,376	1,253	1,003
Nonbarbiturate Sedatives	1,248	962	760	606	396
Antidepressants	3,388	3,343	3,520	3,338	3,426
Antipsychotics	2,643	2,331	2,281	2,167	2,137
Methadone	1,396	1,598	1,506	1,259	1,188
Amphetamines	2,220	2,324	3,020	3,474	2,921
All Other Mentions	63,527	74,544	92,503	103,700	99,667

*Based on data from 441 consistently reporting facilities with adjustments for nonresponse.
Source: NIDA, June 1990 files.

DAWN, a measure of consequences, is often used by some as a proxy for the level of inappropriate prescribing/diversion. Since many of the triplicate programs have been in place for years, one would expect that prescribing would have rebounded to a relatively stable level. To the extent that this is true, the rate of decline in the older triplicate states should not be any greater than in non-triplicate states. However, the decrease has been greater in reporting hospitals in triplicate states than in non-triplicate states. The meaning of this finding is unclear. Regulatory and law enforcement agencies often cite this decline in hospital visits as proof that there have been reductions in inappropriate prescribing and diversion to the street. On the other hand, one investigator has argued that metropolitan areas in states that have triplicate programs actually had a higher average number of mentions per 100,000 visits than did those in non-triplicate states.² A more recent study, using the census population of the metropolitan areas and weighted estimates, shows lower population rates in metropolitan areas in triplicate states.⁴ However, neither study em-

ployed the most appropriate denominator, which is the number of drug users.

Between 1976 and 1985, the number of emergency room episodes involving benzodiazepines decreased 41%, from 24,287 to 14,237. Recent data indicate that the decreases are continuing, but at a slower rate (Fig 1). A large proportion of the recent decrease is attributed to New York. Even before the implementation of the triplicate law in New York, benzodiazepine mentions were decreasing at a substantial rate (Fig 2). Actually, the rate of decrease was somewhat greater before implementation of the triplicate prescription regulation (about 35%) in January 1989 than after implementation (about 30%).

The distribution of benzodiazepine DAWN mentions in New York City by "Reason for Taking Substance"

TABLE VII. Emergency Room Data; Total Number of Emergency Room Episodes and Episodes Associated With Controlled Prescription Drugs According to Year, 1985–1989*

	1985	1986	1987	1988	1989
Total DAWN Episodes	76,391	87,388	103,500	114,411	109,400
Controlled Prescription Drug Episodes	28,840	27,430	27,219	25,292	23,020

*Based on data from 441 consistently reporting facilities with adjustments for nonresponse.

TABLE VIII. Trends for Selected Schedule II Drug Episodes* in DAWN Reporting Hospitals in Triplicate Versus Non-triplicate States

	1985	1986	1987	1988	1989
Episodes in Triplicate States [†]	603	522	477	388	378
Episodes in Detroit	165	196	178	150	87
Episodes in Non-triplicate States	1,206	1,217	1,258	1,198	1,003
Total Number of Episodes [‡]	1,976	1,936	1,911	1,734	1,476

*Codeine, hydromorphone, meperidine, oxycodone.

[†]New York, Buffalo, Chicago, Dallas, Los Angeles, San Diego, San Francisco.

[‡]Excludes national panel.

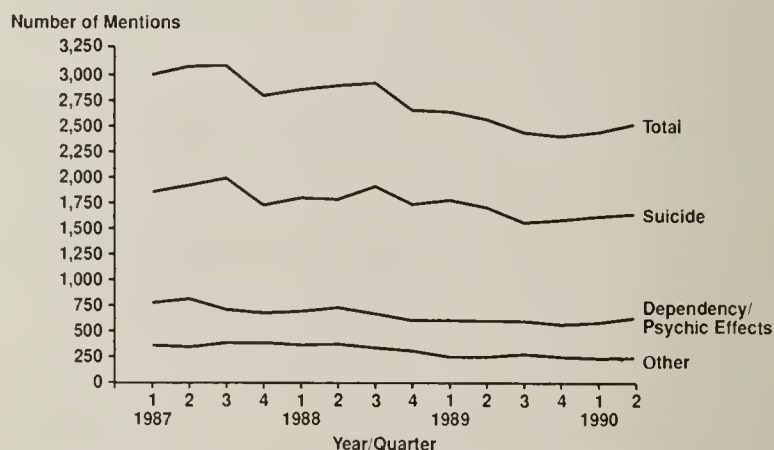


FIGURE 1. National trends in benzodiazepine mentions by reason for taking substance (DAWN data).

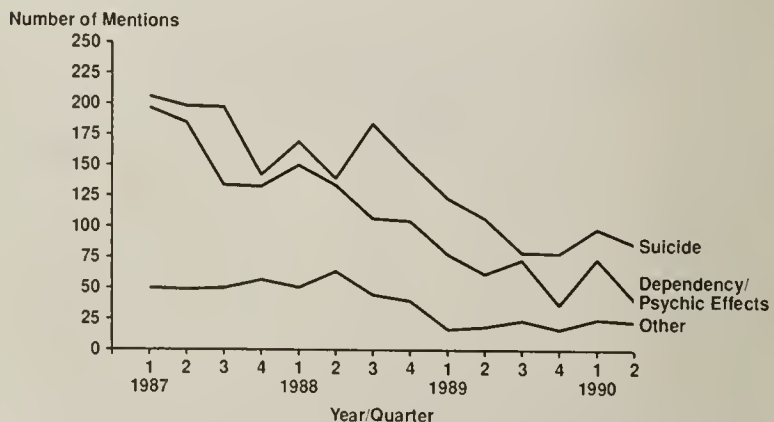


FIGURE 2. Trends in benzodiazepine mentions in New York City by reason for taking substance (DAWN data).

TABLE IX. Distribution of Benzodiazepine Cases in New York City, by Reason for Taking Substance, Before and After Inclusion in Triplicate Program

Motive for Drug Use	1/87-12/88		1/89-9/90		Total DAWN Percentage
	N	Percentage	N	Percentage	
Dependency/Psychic Effects	1,145	39	418	35	24
Suicide	1,363	47	632	53	63
Other	406	14	137	12	13

Source: DAWN.

before and after implementation of the triplicate regulation suggests that the nature of the consequences of use in New York City were different when compared with the rest of the cities in the DAWN system (Table IX). There was a smaller proportion of suicide-related cases compared with the proportion of dependent/psychic-effect cases, which generally reflect abuse. Thus, it could be argued that the consequences of use in New York City were more a reflection of drug abuse because these cases tended to be associated more with males, while suicide cases tend to be associated more with females. In fact, in the DAWN data, the emergency room reports involving drugs that are known to be abused on the street are characteristically approximately 60% male, whereas the suicide cases are characteristically 60% female (Tables X, XI). In addition, most cases are polydrug episodes, with approximately 30% of the cases in DAWN involving alcohol plus another drug. Close to 90% of the dependency/psychic-effect cases are in the age group of the primary drug-abusing population (ie, 20-49 years). In contrast, suicide cases have a larger proportion of persons under 20 and over 50.

TABLE X. Comparison of Characteristics of Benzodiazepine Cases in New York City, Before and After Inclusion in the Triplicate Program. Drug Use Motive: Dependency/Psychic Effects

	Total DAWN 1/89-9/90 (%)	NYC 1/87-12/88 (%)	NYC 1/89-9/90 (%)
Multidrug Episode	80	84	77
Male Patients	51	58	58
<20 y	5	5	3
20-49 y	86	88	86
≥50 y	9	7	11

Source: DAWN.

TABLE XI. Comparison of Characteristics of Benzodiazepine Cases in New York City, Before and After Inclusion in the Triplicate Program. Drug Use Motive: Suicide

	Total DAWN 1/89-9/90 (%)	NYC 1/87-12/88 (%)	NYC 1/89-9/90 (%)
Multidrug Episode	72	64	66
Male Patients	33	35	34
<20 y	8	10	5
20-49 y	79	73	76
≥50 y	13	17	19

Source: DAWN.

TABLE XII. Comparison of Characteristics of Benzodiazepine Cases in New York City, Before and After Inclusion in the Triplicate Program. Drug Use Motive: Dependency/Psychic Effects

Source	Total DAWN 1/89-9/90 (%)	NYC 1/87-12/88 (%)	NYC 1/89-9/90 (%)
Legal Rx	46	28	34
Street Buy	5	11	12
Unknown	43	59	51
Other	6	2	3

Source: DAWN.

The DAWN system collects data by abstracting the emergency room record; therefore, certain variables will have a larger unknown component. This is true for "source of drug." However, dependency/psychic-effect cases have a larger proportion reported as "street buy," whereas suicide attempts and gestures report "street buy" as the source only 1% of the time (Tables XII, XIII).

The differences between dependency/psychic-effect episodes and suicide episodes in terms of sex, age, source, and reasons for contact suggest two distinct populations. DAWN cases that reflect dependency/psychic effects are more likely than suicide cases to be male, age 20 to 49 years, and contacting the ER because of withdrawal, chronic effect, seeking detoxification, and for unexpected reactions. Suicide attempts and gestures do not reflect street abuse and/or diversion and should not be included as evidence of the success of programs whose stated intent is diversion control.

CONCLUSION

Drug abuse, including the abuse of licit psychotherapeutic agents, is a significant problem in this country. However, the problem appears to be improving, and reductions in use are being seen across all classes of drugs. These reductions are beginning to emerge in DAWN for some drugs (such as cocaine) and are continuing for others (such as benzodiazepines). The long-term downward trend in emergency room visits involving benzodiazepines has slowed nationally. However, the decreases in New York City are still significant and now account for a large percentage of the national trend. The decreases are seen in all types of cases—suicides as well as street abuse—and thus do not suggest that the downturns are the result of a program (ie, triplicate prescription) with much specificity. The DAWN

TABLE XIII. Comparison of Characteristics of Benzodiazepine Cases in New York City, Before and After Inclusion in the Triplicate Program. Drug Use Motive: Suicide

Source	Total DAWN 1/89-9/90 (%)	NYC 1/87-12/88 (%)	NYC 1/89-9/90 (%)
Legal Rx	57	43	53
Street Buy	1	1	1
Unknown	37	50	41
Other	5	6	5

Source: DAWN.

data reflect only various consequences associated with the misuse or abuse of drugs. They do not measure in any way whether the acknowledged decrease in prescribing has in fact affected diversion or whether there has been a negative effect on patient care.

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The patient's perspective

REINA BERNER, MSW, ACSW

When new restrictions are imposed on a class of drugs, even for a good reason such as control of drug abuse and diversion, patients with legitimate needs for those drugs are often the ones considered last. The enactment of the regulation that placed benzodiazepines on the New York State triplicate prescription program has had far-reaching effects on patients with epilepsy and on others who experience seizures, muscle spasms, and anxiety and panic disorders. Because of their anticonvulsant properties, some benzodiazepines are widely prescribed for the control of seizures, and we at The Epilepsy Institute have received many letters and phone calls from patients whose ability to get their needed medications has been compromised by the inclusion of benzodiazepines in the triplicate prescription program.

This paper describes the experiences of some of those patients and the difficulties this regulation has caused them, as reported to us. The problems fall into five categories: Issues of confidentiality, difficulties in obtaining needed medications because of physician or pharmacist reluctance to participate in the triplicate program, increased costs for extra doctor visits, added travel time and expense, and employment concerns.

PATIENTS' REPORTED PROBLEMS

Confidentiality. A great many of the patients with the neurologic and psychiatric disorders for which benzodiazepines are prescribed are concerned about the issue of confidentiality. These people are worried, not unjustifiably, that they are being stigmatized by having their names entered into a government-operated computer. One patient writes: "Now I am regarded as a criminal. I am registered on a computer! Does the Department of Health insist the drug dealer fill out three forms? They wouldn't dare. But it's OK to harass the little guy." Another says: "How does the state put my name in a computer that somebody can get access to This could cause me personal problems as well as financial problems I feel as though my civil rights have been violated by being registered with the state without my consent"

The following comment from an angry patient conveys the feelings of fear and frustration which many others affected by this regulation have expressed: "We need less government controls, not more. You won't divulge AIDS carriers, why discriminate against people with brain disorders? You are adding to the mental and

financial anguish of these people who can least afford it!" Another patient says simply, "Whatever happened to my right of privacy?"

There is also concern that a diagnosis may have to be entered in the computer, as well as a name. This is threatening to people with epilepsy because these patients often do not tell their employers about their condition for fear of possible employment discrimination. It is fair to conclude that both the right to privacy and the confidentiality of the doctor-patient relationship are jeopardized by triplicate prescription programs.

Difficulty Obtaining Medication. For patients taking medications on a continuous, long-term basis, difficulty in obtaining medication because of the inclusion of benzodiazepines in the triplicate prescription program is an ongoing, serious problem. The fact is that many doctors will no longer prescribe benzodiazepines. Whether they do not want to be bothered with the paperwork, or are afraid to stock the triplicate prescription pads for fear of being burglarized for them, or simply because, as a consequence of benzodiazepines being included in the triplicate program, they have come to accept the notion that benzodiazepines are somehow more "dangerous," a number of doctors no longer prescribe them.¹ Evidence from the New York State Department of Health confirms this. Thus, some patients are suffering physically, emotionally, and financially.

One patient writes: "I am 71 years old . . . To have to fight for a doctor to prescribe medication so that I can be relieved from awful muscle spasms that prevent me from sitting down, lying down, walking, or sleeping, is sinful. What must we do to reach peoples' hearts and let us live out the remaining days of our lives with some relief from torturous pain?" And this from a person whose disorder had been successfully managed with benzodiazepines: "Because of the state's monitoring, my own doctor has his doubts about giving me the prescription I resent the fact that I have to be made to feel like a criminal when I go and ask for my medication. It is very costly because the medication cannot be renewed We people who suffer these disorders have enough problems without having to worry about getting medication." Finally, another patient writes: "I have painful muscle spasms. My doctor has prescribed Dalmane to help me go to sleep Now, thanks to the New York State Health Department, I have a very hard time getting my medication This is a bad rule and discriminates

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against all people who, for legitimate medical reasons, need this group of medications”

In addition to all of the issues stated here is that of the pharmacy that will no longer fill triplicate prescriptions. Several people mentioned the possibility of buying medication on the street but, aside from being illegal, that alternative is not a viable one for people who need to be under a doctor's supervision when taking these drugs.

Increased Costs for Extra Doctor Visits. After a patient finally works out a system of obtaining medication, there is yet another area to be dealt with—the financial hardship. The restriction on physicians to prescribe for only 30 days at a time means more trips to the doctor for the patient. Suddenly, the twice-a-year visit has become 12 times a year. Depending on the diagnosis, some medications can be prescribed for a 90-day supply. However, Medicaid patients may not receive more than a one-month supply, regardless of diagnosis. It is ironic that the system that is trying to save Medicaid reimbursement expenses by monitoring for drug abuse is adding even more reimbursement expenses by requiring monthly doctors' visits.

“This is crazy to expect sick people to see their doctors more times than required, and the cost is outrageous,” writes one patient. “Can't something be done for us, isn't anyone willing to help?” Another patient explains: “I now must go to a doctor every 30 days for my prescription instead of three or four times a year, so the cost is about \$600 instead of \$200 per year. I was thinking of going to one of those street corners so as not to have to go to the doctor every 30 days, but I was afraid of getting mugged or shot.” A third patient writes: “. . . we lose money when we need to take time off from work to see a doctor every month.” A fourth patient says: “A very bad accident . . . left me with a brain injury. I'm on a medication called Klonopin. Before the regulation, I was able to get it refilled; now I have to get a new prescription every month. I went to three drugstores, and they couldn't get it or didn't want to handle the medication due to the paperwork involved.” Finally, a senior citizen writes: “It has become very hard to get the medicine if I don't go to the doctor. I don't get the prescription, and they are not refillable. Please help. People that require the medication should not be punished by the system. The doctors are frustrated. The patients are depressed. Why?” In summary, as one patient says: “With the new restrictions, I must see my doctor more often to get a new prescription. This costs me additional money, and since I am over 65, it costs Medicare additional money”

Added Travel Time and Expense. The additional amount of time spent traveling to and from the doctor each month further exacerbates the burden placed on the patient. “My doctor is an hour and a half away from my residence (each way) so a visit every 30 days is an all-day affair. This is a bad rule and discriminates against all people who for legitimate medical reasons need this group of medications,” says one patient. Another complains: “The fact that I have to trot up to my doctor—wait till he's available to write the prescription—doesn't count, does it?” A 66-year-old executive reports: “My

physician prescribes medication which is helpful; however, I am limited to a 30-day supply. I must travel for over an hour each way to get to his office each time I need a prescription. I protest this truly unjust ruling This law should be repealed, as it is a hardship and unfair.” For some people, the amount of extra time, the increased costs of transportation, and a compromised physical condition prohibit monthly visits. Without a refillable prescription or a larger supply of drugs, these people may have to go without medication at some point.

Employment Concerns. For people who must take so much time off just to have prescriptions written, employment concerns are commonplace. Many employers perceive these absences as excessive, and the employees are concerned that they may need even more time off should they become ill at some time during the year. One patient writes: “I think that this is too much of an inconvenience to put on the patients who are treated with this medication. It doesn't help anyone, especially me and my family, if I lose my job.” “Very few employers are understanding about monthly doctor visits,” reports another.

CASE REPORTS

Not all of those who wanted their voices heard were able to put their concerns in writing. The following are excerpts from our records of patients who have consulted with us for assistance.

Case 1. A 37-year-old, employed woman living in upstate New York was not able to obtain the medication she required. She did not have the resources to travel to other surrounding counties to try to find a physician who, perhaps, would write the necessary prescription. As a consequence, she was no longer able to function well enough to work and lost her job.

In this case, the issues of human dignity and suffering are significant. To calculate the total loss, one must add the public assistance dollars that the government must now provide to the tax dollars the patient no longer pays because she has no income.

Case 2. A working mother has a daughter with multiple handicaps. The daughter, who receives Medicaid, takes a benzodiazepine to help reduce debilitating muscle spasms. With the new regulation limiting prescriptions to a 30-day supply, both mother and daughter must visit the doctor every 30 days for a new prescription. The daughter loses a day every month from her therapy program, and the mother loses 12 days a year from work. Medicaid pays the bills for increased use of ambulette service and for additional doctors' visits.

Case 3. A 28-year-old man started to have seizures as a sequela to meningitis, which forced him to take what he hoped would be a temporary leave of absence from his position. However, none of the first-line anticonvulsants, alone or in combination, could adequately control his seizures. A benzodiazepine was added to his medication regimen and proved effective. To return to work comfortably without the need to be absent once a month for a doctor's visit, the patient orders and receives the benzodiazepine from out of the country. In this instance, he has been able to negotiate receiving these medicines

at Customs, and less frequently than on a monthly basis. Although he is nervous about this illegal arrangement, and it is costly, his need for the medication has driven him to this extreme solution; in the end he has fewer seizures, and he is able to resume his job and get on with his life.

RESPONSE TO A SURVEY

After benzodiazepines became part of the triplicate program, a telephone survey was conducted by DataTactics, Inc, to determine awareness and attitudes of patients in New York State toward the changes in the prescribing of their medications. Interviews with 367 patients in New York State who were taking benzodiazepines for a variety of disorders took place twice—once in October 1990 and again in January 1991.

Twenty patients who indicated strong negative attitudes toward triplicate prescriptions were called back for in-depth interviews. One of the open-ended questions posed to these patients was: "What alternatives would you consider if you were unable to obtain your current benzodiazepine medication?" Among the answers were the following: See another doctor, pursue other prescription medications, seek drugs from friends and relatives, seek street sources of benzodiazepines, exercise, situation avoidance, alcohol, seek other health-care professionals (eg, dentists) for drug, and acceptance of no benzodiazepine therapy. Some of these responses show the extremes to which some patients would go to get the medications they need.

Patients with chronic medical problems are aware that they need drugs to maintain control of their disorders. The difficulty in obtaining the most effective medication for certain disorders is that many doctors are no longer willing to prescribe benzodiazepines. In some cases, patients have been left without the drugs needed

to control their seizures or muscle spasms. Rather than risk no treatment, these patients will either look for another doctor who will prescribe a benzodiazepine, or they will ask their doctors for a substitute medication. In extreme cases, they seek drugs illegally (ie, from friends or relatives).

CONCLUSION

From the letters we have received, the cases in our files, and the results of the survey, it is evident that the inclusion of benzodiazepines in the triplicate prescription program has had a negative impact on patients. It has impaired access to needed medications by people who have a compelling medical need for these drugs. Patients are angry and frustrated because of the barriers imposed by triplicate prescriptions on benzodiazepines. Some of the people who can benefit the most from the various legitimate medical uses of benzodiazepines are the most silent. Their silence is caused by the feelings of shame and fear that are common among people who have conditions attributed to brain function (eg, epilepsy, cerebral palsy, anxiety, or panic attacks). Now, this already stigmatized population is being singled out again, albeit unintentionally. Most people who have conditions that require the chronic use of drugs do not abuse the drugs. They do not want to take drugs to begin with, and many seek to decrease their dosages.

If patients had as strong a voice as the government agencies, their cries for help could better be heard. When we health care professionals speak out against triplicate programs, we are speaking not only for ourselves, but for our patients as well.

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Filling the knowledge gap: A continuing medical education course on prescribing drugs with abuse potential

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Addiction is a major public health problem in the United States, but medical schools historically have provided little, if any, training in addiction medicine. Although significant gains have been made, medical students still devote less than 1% of their education to learning about this medical problem that will affect one-third or more of their patients.^{1,2} Therefore, many practicing physicians lack knowledge about substance abuse and addiction, do not know how to diagnose and treat it, and lack the skills necessary for managing addicted patients. In addition, many physicians have not been taught specifically how to prescribe to reduce the possibility of addiction, particularly for patients who have a history of abuse.

A case in point is how physicians learn to prescribe drugs, particularly drugs with abuse potential. Medical schools teach primarily the mechanics of prescription writing: where on the prescription to put the patient's name and address, current date, name of the drug (dose, quantity), additional instructions, and the physician's signature. Furthermore, instruction is inadequate for a number of reasons, the first of which is that the content, amount of exposure, and level of instruction is highly variable. Medical students begin to apply prescription writing information during clinical clerkships and may learn more or less about prescribing depending on the medical intern, resident, or attending physician to whom they report and the specific service in which they are placed.

Second, the *Physicians' Desk Reference*, or PDR, the text to which most physicians refer for information about drugs, is made up of package inserts written and submitted by the manufacturers. It does not describe when and how the drug should be prescribed. Moreover, if a drug is off patent and generic versions are produced by many manufacturers, its package insert may not even appear in the PDR because no one company wants to pay to have it included. The alternative is to take the time to find this information, and alternatives that take time are often not selected.

Third, adding drugs that have abuse potential to the knowledge base of prescribing drugs in general compli-

cates the issue even more. What students are most often taught about prescribing drugs with abuse liability are legal matters and warnings. Given that medical school curricula devote so little time to drug abuse education, it is unlikely that students learn how to prescribe all these drugs appropriately, how to monitor patients for abuse, and how to treat patients who do abuse them. There are few continuing medical education (CME) programs that address these educational deficits.³ As a result, many practicing physicians may have even less knowledge about prescribing drugs with abuse potential or have out-of-date or mistaken information. In the extreme, some physicians may be in trouble with the regulatory boards of their states. The consequences are that patients may not receive the medication they need or may receive it in inappropriate or inadequate doses.

ONE EDUCATIONAL APPROACH

We have designed and tested a two-day pilot CME program for primary care physicians to (1) provide them with the information needed to appropriately prescribe drugs with abuse liability, (2) review diagnostic procedures for recognizing addiction, (3) update their knowledge of treatment for dependent or addicted patients, and (4) clarify guidelines for referring patients to addiction medicine specialists. The program encompasses both knowledge and skills and balances and integrates a variety of learning experiences.

The program begins with a series of lectures presented by several different instructors. Core topics include history and epidemiology of substance abuse, pharmacology of the drugs of abuse, and recognition and diagnosis of dependence and addiction. The focus then turns to prescribing practices, treatment of dependence and addiction, and the role of the primary care physician. Because they have a high abuse potential and are sometimes inappropriately prescribed, three classes of drugs are emphasized: narcotic analgesics, sedative-hypnotics, and stimulants. Special topics such as perinatal addiction, dual diagnosis, and prescribing for cancer pain are highlighted. A comprehensive printed syllabus in a detailed outline format is provided for participants so that they can listen during class, rather than concentrate on taking notes. The syllabus also contains a quick reference or trouble-shooting section consisting of one-page summaries of the major topics and simplified diagnostic and treatment procedures tables.

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Interspersed throughout the series of lectures are a variety of other instructional strategies that provide opportunities for active participation. Included are a standardized patient demonstration, a computerized clinical judgment analysis exercise, three computerized clinical case simulations, and group discussions. In general, lecture topics begin with less complex general information and become progressively more specific and detailed. Presentation of single concept topics is followed by a demonstration or simulation to highlight a skill relevant to the topic. For example, after the lecture on recognition and diagnosis of dependence and addiction, the instructor simulates an interview with a "patient" to demonstrate how to obtain a substance-use history and why it is important to prescribing. The physician audience is also asked to participate by asking questions of the "patient." This blend of instructional strategies and learning experiences re-engages participants throughout the program.

Perhaps the most exciting components of the program are the two computer-assisted instructional strategies. The first is a clinical judgment simulation or exercise. In general, a clinical judgment simulation contains a paragraph or two that describes a patient situation and then asks the participant to make a decision about that situation. Embedded in the situation or scenario are five to seven variables that may be important to consider when making the decision called for by the scenario; one or two of the variables may be distractors (eg, neutral to the case). At the end of the scenario, the participant is asked to answer the question posed.

For the simulation, however, each scenario is repeated 16 times to make a set. The patient situation described in the scenario stays the same, and the five to seven variables for decision-making remain constant for all 16, but the values of those variables change from one scenario to the next so that there are essentially 16 different cases. For example, if the variable is blood pressure, the blood pressure readings would be different in each of the 16 cases. The computer randomly generates the values of each of the variables to produce the set of 16 cases. The computer can generate multiple sets. The participant records a judgment response for each case in a set—for 16 judgments. Weights are assigned to each of the variables required to make the judgment and the computer produces a histogram showing the variables and the emphasis placed on each variable to make the decisions across the 16 cases. This histogram is then compared with one produced by an "expert" panel.

This comparison process, which looks at how similar the participants' judgments are to those of the "experts," stimulates lively discussion of where and how participants learned to make these clinical judgments and on what they are basing their decisions. In this program, we use three judgment simulations. The first simulation asks for a judgment regarding the likelihood that the patient described is abusing a particular drug. Similarly, the second simulation asks for a prediction about whether the patient will become an abuser of the prescribed drug. In the third simulation, the question posed is whether or not the patient will benefit from the prescribed medication. This instructional strategy is derived

from the work of Wigton⁴ and was adapted to this program by Dr Roy Poses⁵ of the Medical College of Virginia.

The remaining computer-assisted instructional strategy is the computerized clinical case simulation, which is a format that matches the problem-solving nature of clinical learning. Over the past 20 years, the National Board of Medical Examiners (NBME) has developed CBX, which is a computer-based clinical simulation model.⁶ CBX cases are uncued, with more than 2,000 treatment orders that can be made in free text. In addition, in CBX cases, patients "respond" to treatment in a realistic manner. Aimed at problem-solving and patient management skills, CBX is appropriate to use for multiple levels of learners, from students to practicing physicians. CBX was designed for evaluation purposes, *not* for instruction. However, a collaborative effort resulted in the development of three cases for instructional use for this CME program. The CBX cases, one on pain, the second on anxiety, and the third on attention deficit disorder, complement the three drug classes emphasized in the course.

The CBX cases, each following its corresponding drug class lecture, are interspersed throughout the program. The instructor guides the participants through case simulations in which the physician is responsible for eliciting historical and physical exam findings; for ordering procedures, tests, therapies, and consultations; for scheduling the patient's next appointment; for changing the patient's location; and for reviewing medical charts. The case simulations allow the participants to tie it all together, by using their experience and newly acquired knowledge. At the end of the case, the physician is told which actions and orders helped the patient and which reflected a risk or omission.

In contrast to traditional lectures, this program uses higher levels of learning, such as application and synthesis, when (1) the instructor invites participants to share their own clinical experience, (2) learners are encouraged to articulate their rationale for decision, and (3) learners are challenged to support a chosen route. Via the instructor, medical expertise is modeled, personal experiences in treating patients are shared, errors are explained, thought-provoking questions are asked, and alternative courses of action are suggested. Thus, learners can apply knowledge even before they leave the classroom.

PILOT TEST RECOMMENDATIONS

A pilot test of the program was conducted with a small, representative sample of primary care physicians to evaluate the accuracy and relevance of program content and the blend and delivery of the educational materials and strategies. The pilot test evaluation, conducted by an independent contractor, used multiple questionnaires and structured group interviews with both program participants and a group of observers.

The program syllabus and the standardized patient demonstration were universally praised. More interesting to us, however, was the assessment of the more experimental program components. The evaluation found the clinical judgment analysis simulation to be an intriguing

ing and innovative way to assess and display actual patterns of clinical decision making and, as such, to have significant potential for challenging clinical assumptions, highlighting discrepancies between theory and practice, and generating useful practical discussion. Results of the evaluation revealed (1) that the strongest parts of the program were its syllabus, the skills of the group leaders, and the interactive sessions, particularly the simulated patient; (2) that the computer simulations have great potential as learning strategies in group settings; and (3) that the topic of pain management (prescribing narcotic analgesics) had the greatest potential impact on physician practice behavior. The computerized clinical case simulations based on the NBME model were found to have great potential for integrating knowledge and practice. Three caveats were noted, however. First, the clinical cases need to reflect actual medical practice. Second, the program requires a knowledgeable and facile leader in a large group presentation. Finally, individual preferences in learning style need to be considered. That is, although the clinical case simulations generated were powerful learning tools, some participants found the "groupthink" frustrating at times and would like to have had the opportunity to work on the simulations independently.

SUMMARY

Learning the components of the task of writing a prescription is not the same as learning when to prescribe what drug, in which quantity, dose, and frequency; how to counsel the patient about taking the drug; what to look for while monitoring the patient; and particu-

larly, in the case of controlled drugs, what to do if a patient abuses a medication. Education about prescribing drugs with abuse potential is very limited in medical school, and little exists in the way of continuing medical education. We have designed a two-day continuing medical education course for primary care practitioners that blends a variety of learning experiences and incorporates innovative approaches. This program emphasizes active participation, even within a traditional large group format. Computerized clinical case simulation activities call on participants to draw on their own medical practice experience, and to apply newly acquired knowledge to solve clinical problems before they leave the classroom. The pilot test of the program reinforced how powerful teaching can be when it is led by credible, skillful experts interacting with individuals face-to-face and when it is complemented by small group discussion. Plans for dissemination of this program are under way.

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Panic disorder: Clinical features, neurobiology, and pharmacotherapy

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As a group, anxiety disorders are the most common psychiatric illnesses in the United States today. They have a lifetime prevalence of between 10% and 25%¹ and a six-month prevalence of between 6% and 15%.² In addition to being very common, anxiety disorders are associated with significant impairment in work and social function. The *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) recognizes seven different anxiety disorders, each with its own characteristic type and presentation of anxiety: panic disorder (with and without agoraphobia), agoraphobia without panic, social phobia, simple phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and generalized anxiety disorder.³

Panic is one of the more common and serious types of anxiety, as was demonstrated in a recent study by Weissman et al, who reported that 20% of patients with panic disorder attempt suicide⁴—a suicide rate that exceeds that associated with depression and other psychiatric illnesses. Panic disorder is also the anxiety disorder in which there has been the most scientific progress in understanding the pathophysiology and in developing effective treatments. This paper focuses on panic anxiety and examines information relevant to its clinical presentation, neurobiology, and pharmacotherapy.

CLINICAL FEATURES

The hallmark of panic anxiety is the crescendo-decrescendo or "attack" pattern of the anxiety. The duration of a panic attack may range from minutes to hours. Panic attacks comprise specific physiologic and cognitive symptoms, including shortness of breath, palpitations, dizziness, nausea, sweating, paresthesias, chest pain, and fear of dying. The presence of at least four of these symptoms is necessary to meet criteria in DSM-III-R for a panic attack. In addition, at least four attacks must occur within a four-week period, or one or more attacks must occur followed by at least a month of fear of having another attack, for the condition to qualify as panic disorder (Table I). The first panic attack is often spontaneous, coming "out of the blue" with no discernible direct precipitants.⁵ Other types of panic attacks are termed "nonspontaneous" because a precipitant, such

as a physical or environmental stressful event, is directly associated with the first attack (Table II). In about 60% of cases, a stressful life event occurs within the six-month period before the onset of the first panic attack and may play some role in the onset of the illness (Table II).⁵ We have found that spontaneous attacks tend to dominate the clinical picture early in the course of the illness; over time there is a progression toward more frequent occurrences of nonspontaneous panic attacks.⁵ The first panic attack generally occurs in the patient's mid-to-late 20s, although cases of panic disorder are known to occur in childhood and late in life. Women are more likely to have this disorder; the female-to-male ratio is about two to one.

Typically, panic attacks occur in the context of a clinical syndrome, termed panic-phobic syndrome or panic disorder with agoraphobia, which is made up of three distinct clinical components. First, as noted above, the patient experiences a panic attack. The second component is termed anticipatory anxiety, which is the fear of having another panic attack. Anticipatory anxiety is often founded on the unrealistic belief that panic attacks are potentially life-threatening and therefore should be avoided at all costs. It is the "linchpin" of the panic-phobic syndrome because it often leads to the development of the third component of the syndrome, avoidant behavior. Avoidant behavior may evolve into full-blown agoraphobia, the fear of being in places or situations from which escape might be difficult or in which help is not available in the event of a panic attack. Situations typically avoided are tunnels, bridges, tall buildings, airplanes, crowded places, elevators. We have hypothesized that a realistic appraisal of the first panic attack may result in attenuation of anticipatory anxiety and may prevent or significantly curtail the development of agoraphobia.⁵

Several studies have shown that panic disorder is commonly associated with other psychiatric illnesses particularly major depression.⁶⁻¹³ In one study, we reported that 68% of patients with panic disorder had a history of major depression.¹⁴ Interestingly, 33% of the panic patients had a primary episode of major depression occurring before the onset of anxiety symptoms, suggesting that major depression is not a secondary reaction to having a serious anxiety disorder. Other illnesses that are comorbid with panic disorder are

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TABLE I. Diagnostic Criteria for Panic Disorder

- A. At some time during the disturbance, one or more panic attacks (discrete periods of intense fear or discomfort) have occurred that were (1) unexpected, ie, did not occur immediately before or on exposure to a situation that almost always caused anxiety, and (2) not triggered by situations in which the person was the focus of others' attention.
- B. Either four attacks, as defined in criterion A, have occurred within a four-week period, or one or more attacks have been followed by a period of at least a month of persistent fear of having another attack.
- C. At least four of the following symptoms developed during at least one of the attacks:
- (1) shortness of breath (dyspnea) or smothering sensations
 - (2) dizziness, unsteady feelings, or faintness
 - (3) palpitations or accelerated heart rate (tachycardia)
 - (4) trembling or shaking
 - (5) sweating
 - (6) choking
 - (7) nausea or abdominal distress
 - (8) depersonalization or derealization
 - (9) numbness or tingling sensations (paresthesias)
 - (10) flushes (hot flashes) or chills
 - (11) chest pain or discomfort
 - (12) fear of dying
 - (13) fear of going crazy or of doing something uncontrolled
- Note: Attacks involving four or more symptoms are panic attacks; attacks involving fewer than four symptoms are limited symptom attacks.
- D. During at least some of the attacks, at least four of the C symptoms developed suddenly and increased in intensity within ten minutes of the beginning of the first C symptom noticed in the attack.
- E. It cannot be established that an organic factor initiated and maintained the disturbance, eg, amphetamine or caffeine intoxication, hyperthyroidism.
- Note: Mitral valve prolapse may be an associated condition, but does not preclude a diagnosis of Panic Disorder.

alcoholism, obsessive-compulsive disorder, and childhood separation disorder.⁵

NEUROBIOLOGY OF PANIC DISORDER

Neuroanatomy. Although the neuroanatomic basis of anxiety disorders has not been fully elucidated, in vivo brain imaging techniques such as positron emission

TABLE II. Nature of First Panic Attack and Associated Life Events in 60 Patients with Panic Disorder¹⁵

	No. (%) of Patients
Onset of attack	
Spontaneous	47 (78)
Nonspontaneous, precipitated by:	13 (22)
Public speaking	3
Stimulant drug use	3
Family argument	2
Leaving home	2
Exercise (while pregnant)	1
Being frightened by a stranger	1
Fear of fainting	1
Stressful life events associated with attack	
No stressful life event within 6 mo	22 (37)
Stressful life event within 6 mo*	38 (63)
Threatened or actual separation from important person	11
Change in job causing increased pressure	8
Pregnancy	7
Move	5
Marriage	3
Graduation	3
Death of close person	3
Physical illness	2

*Four patients had two concomitant stressful life events.

tomography (PET) and single photon emission computed tomography (SPECT) offer promise in determining which brain structures may be involved in the pathophysiology of anxiety disorders. Reiman et al¹⁵ induced anticipatory anxiety in healthy controls by shock threat during PET imaging with the blood flow tracer 15-oxygen and found that there was a significant blood flow increase in the bilateral temporal poles. In a related study, Reiman et al¹⁶ induced panic anxiety in patients with panic disorder by infusing lactate and, during the panic attacks, assessed cerebral blood flow with 15-oxygen PET. They found that there was an increase in blood flow to the temporal cortex. Thus, two of the principal components of the panic-phobic syndrome, panic attacks and anticipatory anxiety, may be localized to the temporal cortex.

Neurochemistry. Several neurotransmitter systems have been implicated in normal and pathological anxiety, including the serotonergic, glutaminergic, and peptidergic systems. Perhaps the two systems that have been most extensively investigated in both preclinical and clinical studies are the noradrenergic and the γ -aminobutyric acid (GABA)/benzodiazepine receptor system. With regard to the noradrenergic system, electrical stimulation of the locus ceruleus (LC), the major norepinephrine-containing nucleus in brain, produces a fearing-like state in nonhuman primates.¹⁷ Lesioning of the LC attenuates fear and anxiety-like responses in monkeys.^{18,19} In addition, drugs that increase norepinephrine turnover cause anxiety states in healthy humans.^{20,21} We demonstrated that yohimbine, an α_2 -adrenergic autoreceptor antagonist that increases norepinephrine turnover, produced greater increases in anxiety in patients with panic disorder as compared with healthy controls.²² Moreover, the patients with a history of frequent panic

attacks had significant elevations in plasma MHPG, a norepinephrine metabolite, after yohimbine administration as compared to the controls. Yohimbine-induced increases in plasma MHPG were significantly related to patients' anxiety ratings.²² These data provide support for the hypothesis that panic anxiety may be related to altered noradrenergic function.

In 1977, two groups of investigators discovered the presence of saturable, high-affinity, stereospecific binding sites for benzodiazepines in rat brain.^{23,24} Soon after this discovery, it was learned that the so-called benzodiazepine receptor was coupled with a receptor for GABA, the major inhibitory neurotransmitter, and these two recognition sites formed a supramolecular complex with chloride ion channel and functioned to regulate the conductance of chloride ions across cell membranes (for review see references 25 and 26). It is now known that all of the major pharmacologic actions of benzodiazepines (anxiolytic, muscle relaxant, anticonvulsant, and sedative hypnotic) are mediated through this receptor complex.

The evidence implicating the GABA/benzodiazepine receptor in normal and pathologic anxiety includes studies of the highly selective benzodiazepine receptor antagonist β -carboline-3-carboxylate ethylester (β -CCE). In primate studies, β -CCE produced intense anxiety, an effect that was blocked by administration of benzodiazepine drugs.^{27,28} In addition, Dorow et al²⁹ found that a β -CCE analog, FG-7142, produced extreme anxiety in humans that was strikingly similar to panic anxiety (Table III). The FG-7142-induced anxiety syndrome included motor tension, autonomic hyperactivity, extreme subjective apprehensiveness, and increases in heart rate, blood pressure, and plasma cortisol. The effects were so intense that a benzodiazepine drug was administered to the subjects to attenuate the anxiety, and the human studies were discontinued. Other agents that provoke anxiety responses in panic patients include caffeine,³⁰ carbon dioxide,^{31,32} and lactate.^{33,34}

PHARMACOTHERAPY

Three types of medications have proven effective for panic disorder: some tricyclic antidepressants (imipramine is the tricyclic that has been most extensively investigated in panic disorder),³⁵⁻³⁸ monoamine oxidase inhibitors (eg, phenelzine),^{35,37,39,40} and the benzodiazepine drugs, particularly the high-potency benzodiazepines such as alprazolam and clonazepam.^{35,41,42} The only agent that has been approved by the FDA specifically for treatment of panic disorder is alprazolam. Approval was granted after a large, multicenter, double-blind controlled study of alprazolam in 526 patients with panic disorder or panic disorder with agoraphobia.⁴¹ The study consisted of an eight-week comparison of alprazolam versus placebo. Medication was administered in a flexible dosing schedule. The end point analysis revealed that 55% of patients randomized to alprazolam were panic-free as compared with 32% of patients randomized to placebo treatment. Alprazolam demonstrated superiority for both spontaneous and nonspontaneous panic attacks. It is also effective for accompanying anticipatory and generalized anxiety.

TABLE III. Effects of Benzodiazepine Receptor Agonists and Antagonists on the Symptoms of Anxiety

DSM-III Criteria for Generalized Anxiety Disorder	Benzodiazepine Agonist Effects [†]	Benzodiazepine Active Antagonist Effects [‡]
Motor Tension		
Shakiness, jitteriness, trembling	↓	↑
Muscle aches, tension	↓	↑
Fatigability	—	—
Fidgeting, restlessness	↓	↑
Autonomic Hyperactivity		
Heart pounding, racing	↓	↑
Dizziness	—	—
Light-headedness	↓	—
High respiratory rate	?	—
Paresthesias	?	—
Upset stomach	?	↑
Frequent urination	?	↑
Sweaty, cold, clammy hands	—	—
Flushing	—	↑
Apprehensive Expectation		
Anxiety	↓	↑
Fear, worry	↓	↑
Anticipation of misfortune	↓	↑
Vigilance and Scanning		
Insomnia	↓	↑

*Adapted from Greenblatt DJ, Shader RI: *Benzodiazepines in Clinical Practice*. New York, Raven Press, 1974.

†Adapted from Dorow R, Horowski R, Paschelke G et al: Severe anxiety induced by FG-7142, a beta-carboline ligand for benzodiazepine receptors. *Lancet*. 1983;1:98.

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Outcome and Relapse. An important issue relevant to the pharmacotherapy of panic disorder relates to long-term outcomes and relapse rates after discontinuation of treatment. Available data suggest that tolerance to the antipanic effects of tricyclics and high-potency benzodiazepines does not develop during long-term treatment,^{35,36,38,43-46} although tolerance may develop to monoamine oxidase inhibitors.⁴⁷ Nagy et al⁴³ followed 60 patients with panic disorder for a mean of 2.5 years after they had been treated with alprazolam and group therapy for four months. Thirty percent were no longer using medication, and 70% were still taking alprazolam. There was no evidence of attenuation of alprazolam's efficacy or tolerance over the follow-up period. In fact, 60% were receiving lower doses of alprazolam compared with their index doses, and only 5% were receiving the same dose that they received at index. Significant functional gains over the follow-up period were reported.

The majority of short-term and long-term treatment studies indicate that there is a substantial relapse rate after the discontinuation of pharmacotherapy. In a recent review of imipramine and phenelzine treatment studies, Noyes and Perry⁴⁸ found that between 26% and 70% of patients treated with imipramine and approximately 14% to 100% of patients treated with phenelzine relapsed after cessation of treatment. A comparable rate is anticipated for benzodiazepine treatment, although precise information is not available. It is now suggested

that in cases where good symptom control is achieved, treatment of panic disorder continue for a minimum of six months and perhaps as long as nine months. Longer intervals may be necessary if response is inadequate or relapse occurs during discontinuation.

Benzodiazepine Withdrawal. A significant issue related to use of benzodiazepines for panic disorder is the occurrence of a withdrawal syndrome on drug discontinuation. Roy-Byrne⁴⁹ found that after a six-week, double-blind trial of placebo, alprazolam (average daily dose 4.3 mg), and diazepam (average daily dose 56 mg) and a two-week taper, 69% of alprazolam-treated and 33% of diazepam-treated patients experienced withdrawal syndromes. In a multicenter, eight-week trial of alprazolam, Swinson et al⁵⁰ found that 22% of alprazolam-treated and 4% of placebo-treated patients experienced a withdrawal reaction over a four-week taper period. Other investigators have also reported withdrawal syndromes after benzodiazepine treatment of panic disorder.^{51,52}

The factors that predict a withdrawal syndrome secondary to benzodiazepine discontinuation include older age (>60 years), history of withdrawal from other agents, longer duration of treatment, rapid withdrawal from a high daily dose, and short- and intermediate-duration benzodiazepines.⁵³ It is clear that a longer taper period than that previously recommended is required for benzodiazepine discontinuation. Davidson⁵³ recommends a rate of withdrawal for alprazolam and clonazepam of 0.25 mg to 0.5 mg per week over a period of between 4 to 24 weeks.

Several pharmacologic strategies to prevent benzodiazepine withdrawal reactions are presently under investigation. Several agents including propranolol,⁵⁴ buspirone,^{55,56} and clonidine,⁵⁷⁻⁵⁹ have been examined as treatments of benzodiazepine withdrawal, with unimpressive results. In a recent double-blind, placebo-controlled study, Schweizer et al⁶⁰ found that five weeks after benzodiazepine taper, patients assigned to carbamazepine were more likely to be benzodiazepine-free as compared with patients assigned to placebo during the taper. There was a trend for carbamazepine to demonstrate less severe withdrawal effects as compared with placebo. More information is required before pharmacologic approaches to treating benzodiazepine withdrawal can be recommended.

Choosing a Treatment Strategy. Because three classes of agents have proven efficacy for panic disorder, the choice of treatment is determined by a variety of issues including side effects, time course of efficacy, presence of concomitant syndromes such as major depression and generalized anxiety disorder, suicide potential, and concerns about withdrawal reactions (Table IV). In general, benzodiazepines, in comparison with the antidepressants, have fewer cardiovascular side effects, produce greater levels of sedation (particularly early in treatment), have a more rapid onset of action, are effective for anticipatory and generalized anxiety symptoms, are less lethal in overdose, and may produce rebound anxiety and even seizures with abrupt discontinuation. The antidepressants are associated with cardiovascular side effects, may produce anxiety symptoms in some patients but are less sedating, have a longer onset

TABLE IV. Comparison of High-Potency Benzodiazepines and Antidepressant Agents (Tricyclics/Monoamine Oxidase Inhibitors) for the Treatment of Panic Disorder

	Benzodiazepines	TCA/MAOI
Effective treatment for panic Attacks	Yes	Yes
Effective for concurrent major Depression	?	Yes
Effective for concurrent generalized anxiety/anticipatory anxiety	Yes	No
Time course for efficacy	Early (5-10 days)	Later (2-4 weeks)
Associated with withdrawal reaction	Yes	Less common
Cardiovascular side effects	No	Yes
Associated with sedation	Yes	No
High lethality in overdose	No	Yes

of action, are effective for concomitant depressive episodes, are more lethal in an overdose, and tend not to be associated with withdrawal reactions.

SUMMARY

Anxiety disorders are common, debilitating illnesses. Panic disorder is an anxiety disorder with a characteristic clinical presentation. A growing body of neuroanatomical and neurochemical data is beginning to elucidate its pathophysiology. There are currently three types of effective pharmacotherapies for panic disorder: tricyclic antidepressants, monoamine oxidase inhibitors, and high-potency benzodiazepines. The choice of a pharmacologic approach may be guided by considerations of potential side effects and other clinical/pharmacologic concerns.

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Benzodiazepine use/abuse: An epidemiologic appraisal

A comparison of data from 1979 and 1990 US National Household Surveys on the use of psychotherapeutic medications indicates that (1) the past-year prevalence rate for the use of anxiolytics, primarily benzodiazepines, has declined significantly; (2) the decline has come mainly at the expense of people who clearly merit psychiatric treatment; and (3) the decline has not been compensated for by use of other medications or nondrug therapies. More importantly, the data argue that the decline in use has occurred in circumstances in which there has been significant underutilization of benzodiazepines: In both the 1979 and 1990 studies, use rates for benzodiazepines were very low relative to the proportion of population with defined clinical need. Results also indicate that the proportion of medical users of benzodiazepines who advance their own dosage is very low, and is equivalent to that of patients being treated with antidepressants. Thus, the infrequent tendency to increase the dose seems to be characteristic of the patient, rather than of the medica-

tion. On the basis of patient reports, the benefit/risk ratio for benzodiazepines is very good and there is little evidence of serious abuse. Data from studies of new admissions to methadone maintenance programs do not support the contention that there is either widespread or persistent abuse of benzodiazepines among narcotic addicts. Contrary to popular belief, the demand for benzodiazepines among narcotic addicts is not high.

(Manuscript in preparation)

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Consequences of the 1989 New York State triplicate benzodiazepine regulation

We compared psychoactive medication prescribing and Medicaid expenditures before (1988) and after 1989–1990 institution of the New York State (NYS) triplicate benzodiazepine regulations. Data were obtained from the Geographic Prescription Audit of IMS America, NYS Medicaid, and Blue Cross/Blue Shield (BC/BS). From 1988 to 1989, NYS benzodiazepine prescribing decreased by 44%, 60%, and 30% as assessed by IMS, Medicaid, and BC/BS, respectively. In the first half of 1990, Medicaid benzodiazepine prescribing fell further to 29% of the comparable 1988 level. Medicaid benzodiazepine expenditures decreased 52% from 1988 to 1989 (\$21.7 million to \$10.4 million), whereas alternative sedative-hypnotic expenditures increased 115% (\$3.9 million to \$8.4 million). Total Medicaid psychoactive medication expenditures remained nearly constant (\$48.7 million to \$45.6 million). Prescribing of alternative sedative-hypnotics increased in NYS compared with decreases nationally (IMS data)

(eg, meprobamate +125% vs -9%; methyprylon +84% vs -15%; ethchlorvynol +29% vs -18%; butabarbital +31% vs -15%; hydroxyzine +15% vs -1.1%; and chloral hydrate +136% vs -0.4%). Increased prescribing of alternatives was also seen in the Medicaid and BC/BS data. Although the triplicate regulation has decreased benzodiazepine prescribing, an undesirable increase has occurred in the prescribing of less acceptable medications. The wider public health, patient care, and financial implications of these regulations are of concern and require further study.

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The clinician's perspective of triplicate prescription

In 1986, the New York State Department of Health identified an imminent danger to the public health from benzodiazepine misuse. Critical review of all of the Department of Health documents failed to substantiate this view.

The enactment of the triplicate prescription rule has had a profound effect on physician prescribing habits. This chilling effect on prescribing patterns by physicians is based on several factors. The Department of Health used no scientific drug utilization review policy in highlighting possible overprescribers. Having these valuable triplicate prescription blanks makes physicians targets for theft. Patients may not obtain medication for more than 30 days, and there are no permitted refills. If the patient's diagnosis is written on the face of the prescription, a 90-day prescription may be written. In a move toward defensive medicine, physicians are now sending patients for unwarranted psychiatric consultations. This does nothing for patient care but does drive

up the cost of medical care in an already overburdened system.

Benzodiazepines were developed as safe replacements for drugs such as meprobamate, glutethimide, and chloral hydrate. Unfortunately, physicians in New York are turning to these preparations with greater frequency as benzodiazepine are prescribed less.

Buspirone had an initial upsurge in use, and that has fallen off as patients and physicians learn that this drug is not effective after benzodiazepine administration.

The illnesses of anxiety, panic, and insomnia will not disappear because of a new rule of regulation. The Department of Health equates the disease of addiction with dependence. They are not equivalent. As benzodiazepine mentions in the emergency rooms of New York fall, alcohol in combination mentions rise. This is not a surprising fact since both chemicals can bind to the same receptor in the brain.

(Manuscript in preparation)

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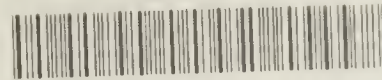
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